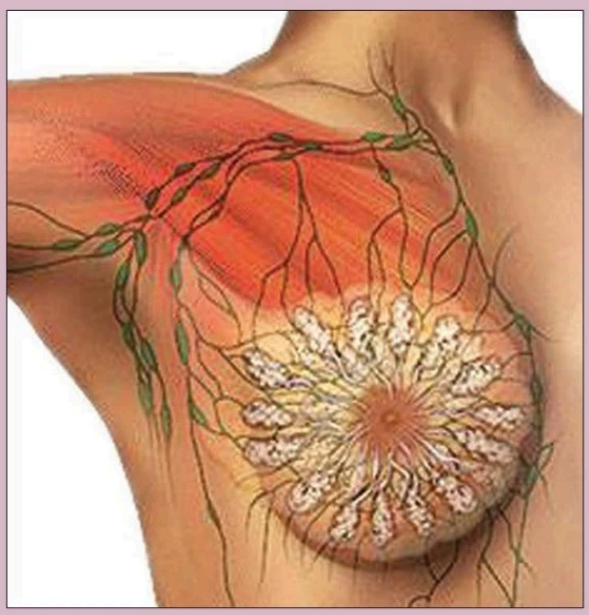
Chapter-01

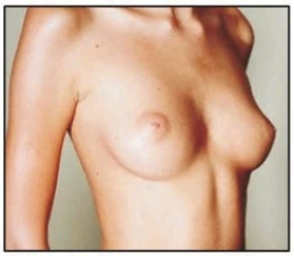
Female Breast Anatomy and Physiology



Embryology
Gross Anatomy
Lymphatic Drainage
Blood Supply & Lactation

Objectives

- To understand the development of the breast and possible abnormalities occurring during development.
- To understand the anatomical and histological structure of the breast with possible abnormalities.
- To understand the physiological changes occurring in breast during menstruation, pregnancy, lactation and menopause.
- To understand the effects of various hormones on the breast.
- To understand various modes of spread of diseases of breast specially



FEMALE BREAST ANATOMY & PHYSIOLOGY

Shuja Tahir, FRCS, FCPS

EMBRYOLOGY

Breast (mammary gland) is derived from the ectoderm and becomes apparent in the embryo 4 mm in length as a mammary bud. The mammary bud and surrounding tissue thickens to become mammary ridge by the time embryo is 7 mm long.

There is no sign of future breast in the embryo before first four weeks of gestational period.

(5TH WEEK) 35TH GESTATIONAL DAY

Epithelial mammary bud appears by 35th gestational day. Two linear ectodermal thickenings develop on the ventro-lateral surface from armpit to groin in the young embryo by 37th day. These are called milk ridges or milk lines.

Several mammary glands develop from these ridges in lower animals. Only two small buds are seen at future breast areas and the ridge disappears in human female. Intrauterine development of breast is similar in both sexes.

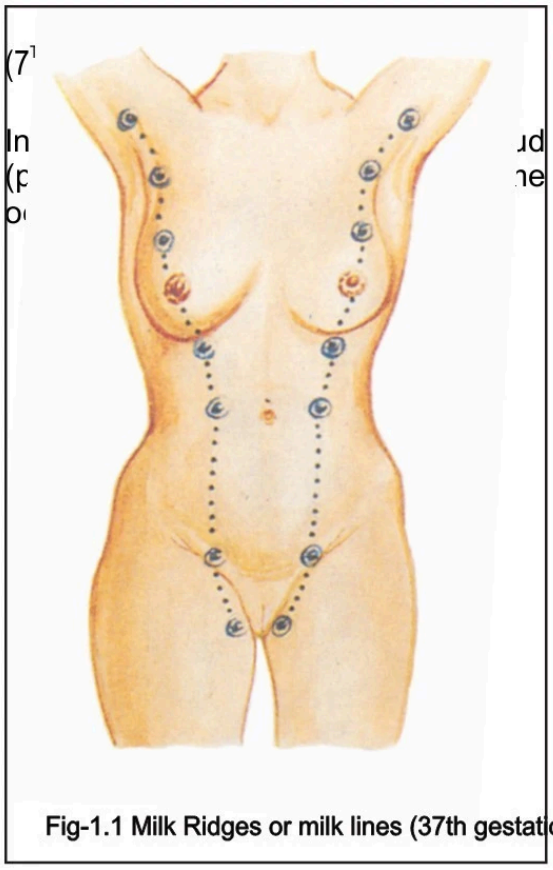


Fig-1.1 Milk Ridges or milk lines (37th gestational day)

The epithelial cells on the deeper

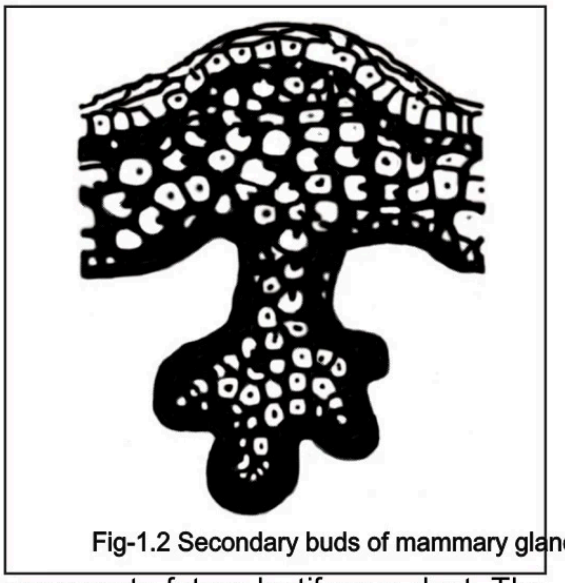


Fig-1.2 Secondary buds of mammary gland

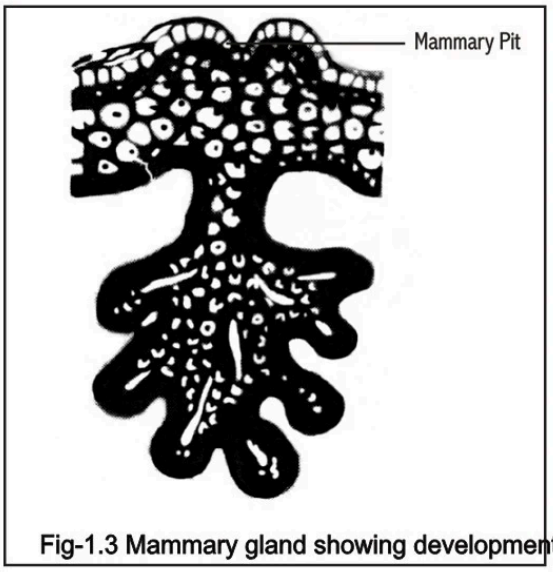


Fig-1.3 Mammary gland showing development of nipple

represents future lactiferous duct. The epidermal and epithelial buds grow into the depth on both sides.

These are surrounded by the underlying mesenchyme. The depressed ectodermal thickening is raised to form nipple. The mammary glands collectively form the future breast.

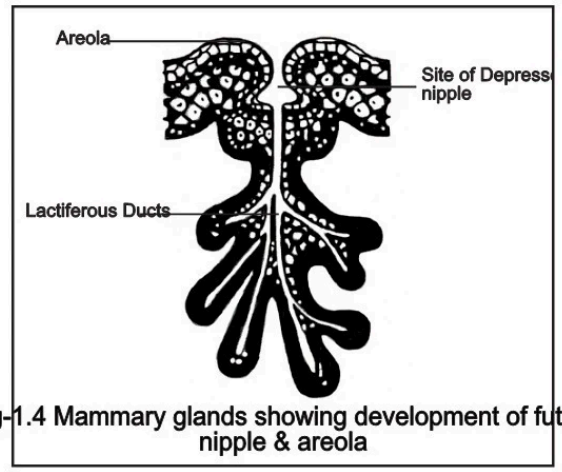


Fig-1.4 Mammary glands showing development of future nipple & areola

(8^{TH} WEEK)
56^{TH} - 150^{TH} GESTATIONAL DAYS

Nipple formation begins at 56^{th} gestational day, mammary ducts develop at 84^{th} gestational day and canalization occurs by 150^{th} gestational day.

DEVELOPMENTAL ANOMALIES

Following development anomalies may occur;

Non development of breast but development of Nipple **(Amazia).**

Non development of nipple and breast (Amastia).

Accessary breast tissue present along milk line (Polymastia).

Accessary nipple present along milk

GROSS ANATOMY AT BIRTH

The rudimentary breasts are identical in both sexes at birth and for few years afterwards.

The breast or the mammary glands are modified skin glands which are embedded in the fatty tissue.

The mammary gland or breast in fact is conglomeration of 15 to 25 individual and independent glands having separate lactiferous ducts.

The adult female breasts are paired sub-cutaneous organs on the anterior thorax lying completely within the superficial and deep layers of superficial pectoral fascia.

Adult female breast is mature breast and is of different size and shape in different women. The size and shape depends upon genetic, racial and dietary factors together with age, parity and menopausal status of the women. The size of the base of the breast is fairly constant in almost all women.

The breast lies in front of 2nd to 6th rib in the mid clavicular line. The breast lies over the pectoralis major muscle and extends to serratus anterior and external oblique muscle of the abdomen.

Axillary tail is lateral extension of breast tissue into axilla. Both breasts consist of nipple, areola and breast tissue.

The mesenchymal tissue present around growing ductal tissue changes into dense connective tissue dividing the whole breast into 15-25 lobes.

There are about 15-25 main mammary ducts in each breast. These open on the summit of the nipple through separate openings. Each duct has dilated part called ampulla just before its opening on to the nipple.

Each main duct drains a lobe of the breast. Each lobe is further divided into lobules and acini. Each lobe is irregularly lobulated.

Each lobule has a collection of 10-100 acini or terminal ductal lobular units. It consists of extra and intra lobular terminal ductule, alveoli, terminal ductal lobular units [TDLU]). Some secretions are also present in these ductules.

Non lactating breast consists of more fibrous tissue and less glandular tissue (almost only ducts).

The growth of mammary tissue beneath the areola occurs at the age of 10 years. It is called breast bud. True nipple develops at about 12 years of age followed by 2-3 years growth of breast tissue. Then there is areolar recession and the breast takes a classical shape.

The size of breast in females enlarges at puberty by the action of oestrogens. The areola becomes recognizable as

The nipple has myoepithelial cells (erectile tissue) in its dermis which makes the nipple erect on stimulation.

Areola has sweat glands, and subaceous glands present in its dermis. The sebaceous glands enlarge during pregnancy and are called tubercles of Montgomery.

Fascia is present beneath the breast which is the continuation of the fascia of Scarpa (sub mammary fascia). Sub mammary space is present between this fascia and fascia over pectoralis major muscle. The fascia is continuous above with superficial cervical fascia and below with Camper's fascia. Lymphatic plexus is present in the sub mammary space.

Young breast has fibrous tissue strands which connect deep fascia with deeper layers of the dermis. These are called ligaments of Astley Cooper. These keep the breast protuberant and well shaped.

These strands get atrophic in elderly women and breasts become pendulous.

Peau-de-Orange (like orange peel) appearance is produced in carcinoma and inflammatory conditions of the breast due to presence of dermal edema in between these ligaments.

The development of female breast begins at puberty stimulated by estrogens of monthly cycles. There is stimulation of stromal and ductal growth. There is deposition of fat to give mass to adult breast.

The additional growth of breasts occur during pregnancy when glandular tissue develops completely to produce milk. It happens due to stimulatory effects of large quantities of placental estrogens. These lead to proliferation and branching of ductal system. Additional quantities of growth hormone and prolactin lead to growth and branching of ductal system. Gluco-corticoids and insulin also have some role in this process of proliferation. Stromal tissue of breast increases and the deposition of fat also increases simultaneously.

The large quantities of placental progesterones stimulate growth of lobules, budding of alveoli and development of secretory characteristics of alveolar cells during pregnancy.

Both estrogens and progesterones are essential for the physiological development of breast. Both estrogens and progesterone hormones have inhibitory action on actual secretion of milk.

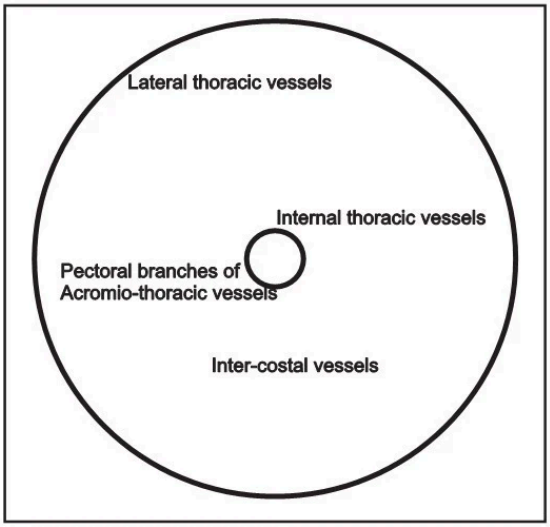
Prolactin, a hormone secreted by the anterior pituitary gland promotes secretion of milk. Prolactin secretion starts by fifth week of pregnancy and its serum concentration steadily increases till the birth of baby when the hormonal

LATERAL THORACIC ARTERY

It is a branch of axillary artery. It supplies the superior part of the breast.

INTERNAL THORACIC ARTERY

It is a branch of subclavian artery. It supplies through its perforating branches specially through 2nd and 3rd intercostal spaces. These branches are large size in adult females.



INTER COSTAL ARTERIES

These supply through their perforating branches.

PECTORAL BRANCHES

These are branches of acromio-thoracic artery which is a branch of axillary artery. These supply upper part of the breast.

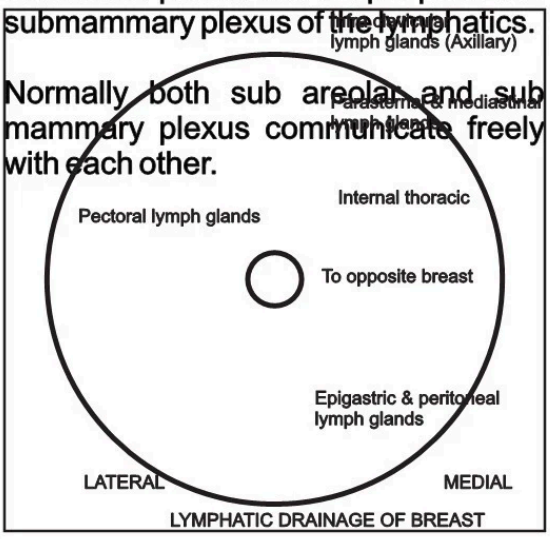
VENOUS DRAINAGE

Venous drainage is via veins accompanying the arteries.

LYMPHATIC DRAINAGE OF THE BREAST

Lymph capillaries make network with surrounding lymph capillaries, lymphatics from the opposite breast, lymphatics from the abdominal wall and neck.

Superficial parts of the breast drain into subareolar plexus and deeper parts into submammary plexus of the lymphatics.



LYMPHATIC DRAINAGE OF BREAST

Normally both sub areolar and sub mammary plexus communicate freely with each other.

There are three pathways of lymphatic

AXILLARY GROUP OF LYMPH GLAND

These glands are about 35-50 in number. These are placed in five groups;

1. Anterior or pectoral group.
2. Posterior or subscapular group.
3. Lateral group.
4. Central group.
5. Apical group.

The axillary and transpectoral pathways communicate directly and indirectly with one another through supra and infra clavicular lymph glands.

Axillary group of lymph glands drain the major part of the breasts. Most of the regional spread from carcinoma of the breast is seen here.

Metastatic deposits can be present in the other groups of lymph glands but these usually appear after the axillary involvement.

Most of the lymph from subareolar and submammary plexus is drained to the anterior or pectoral group of axillary lymph glands.

Axillary tail drains into the posterior or subscapular group of axillary lymph glands.

Upper convexity of the breast drains into infra clavicular group.

Medial part of the breast is drained by sub mammary plexus of the opposite breast and also to the lymph glands along the internal thoracic artery and from these to the mediastinal lymph glands.

The inferior part of the breast is drained by the lymphatics of abdominal wall and to the extra peritoneal lymphatic plexus.

All these groups of lymph glands can be involved in the metastasis of the carcinoma breast. Their involvement is seen in various levels such as;

Level-I
Involvement of axillary node (lateral) below to pectoralis minor muscle.

Level-II
Involvement of nodes behind (posterior) pectoralis minor muscle.

Level-III
Involvement of nodes above (supro-medial) the pectoralis minor muscle.

LACTATION

Both estrogens and progesterones are essential for the physiological development of breast. Both estrogen and progesterone hormones have inhibitory action on actual secretion of milk.

Prolactin, a hormone secreted by the anterior pituitary gland promotes secretion of milk. Prolactin secretion

secretion of mother in surges. Growth hormones, cortico-steroids and parathyroid hormone are also involved in lactation.

There is rapid growth and branching of terminal portions of the gland. There is some loss of interstitial adipose tissue. The visible enlargement of breast is noticed two months after pregnancy.

The nipples increase in size. The areola becomes bigger and pigmented. The ductal system increase in number and size during first two trimesters. True glandular acini required to produce milk appear during early part of 3rd month. The differentiation of acini for secretary activity occur during last trimester.

The enlargement of breasts during last month of pregnancy is due to hypertrophy of parenchymal cells of alveoli with a hyaline eosinophylic, proteinaceous secretion termed colostrum. About 3 days post partum, the fat content of colostrum increases suddenly to change it into typical milk secretion.

The lactating breast is obvious. The nipples project as much as 02 cm beyond aerola.

There are 15-20 sinuses engorged with milk which lie beneath the aerola. The milk is easily sucked by the baby's gums and lips pressure. Many ductules connect these sinuses with peripheral alveoli. All these alveoli and ductules are surrounded by myofibrils and smooth muscles.

There is rich capillary and lymphatic bed surrounding the alveoli binding these with lactating cells.

The blood supply through the lactating mammary gland is 400-4500 times the volume of milk secretions. The increased rate of blood flow increases the rate of milk secretion.

The growth and function of the breast depends upon integrated actions of pituitary, ovarian, thyroid and adrenal glandular hormones. Growth of mammary ducts depends on estrogen synergized by growth hormone, prolactin and adreno-cortico-steroids.

The development of lobulo-alveolar glandular system requires both estrogen and progesterone in the presence of prolactin. Lactogens and milk secretion are regulated by prolactin and corticoids.

Ovarian steroid 17α estradiol and progesterone are essential for mammary gland development in females. No breast changes are seen in girls with gonadal dysgenesis at puberty.

Oral contraceptives increase the breast size. The oophorectomy doesn't affect the size of breast after complete development.

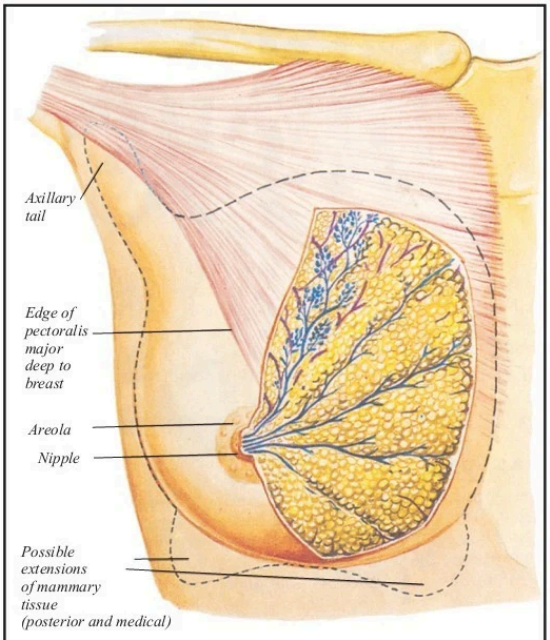


Fig-1.5 Anatomy of Breast

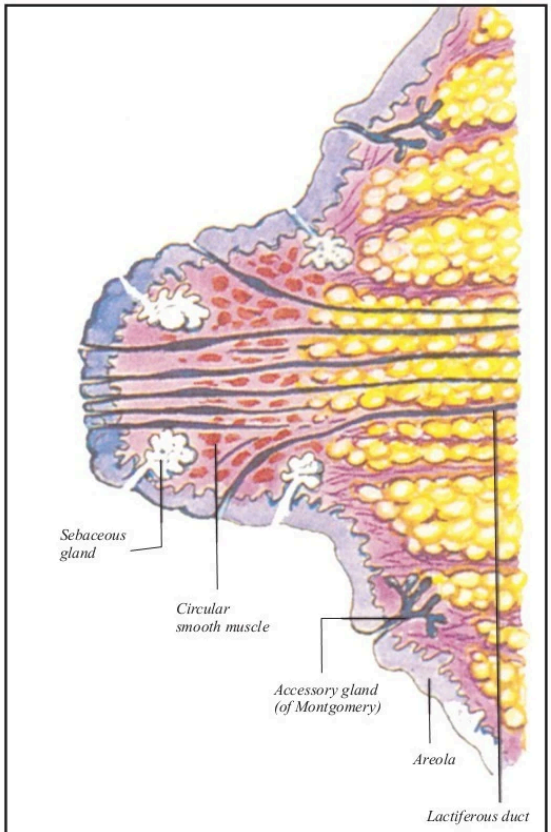


Fig-1.7 Anatomy of nipple

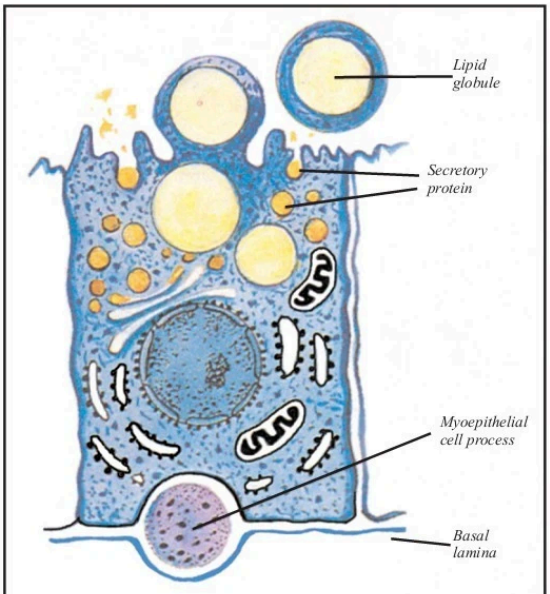


Fig-1.6 Ultra structure of secretory cell of breast

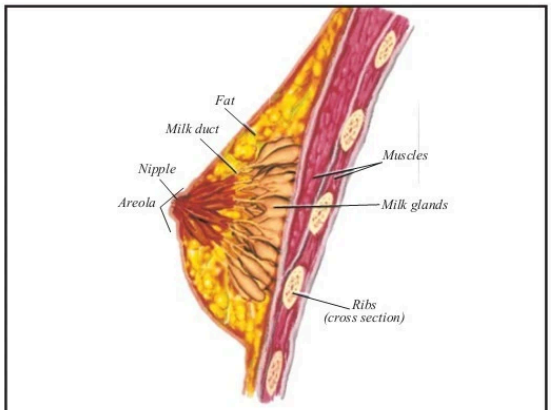


Fig-1.8 Anatomy of Breast

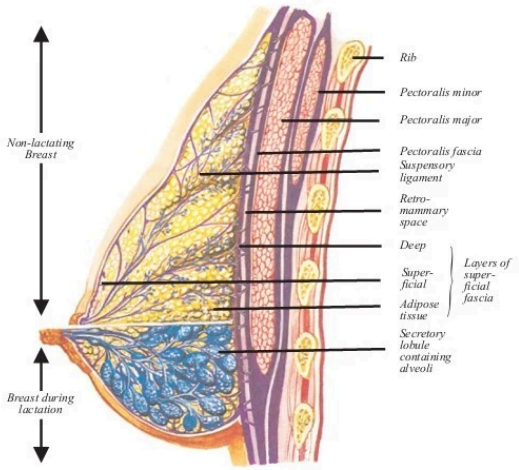
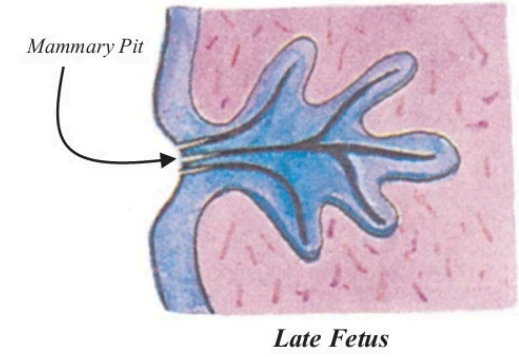


Fig-1.9 Anatomy of Breast

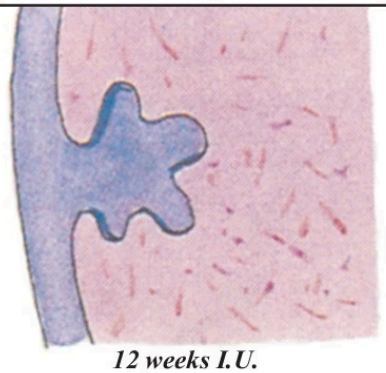
Neonate

Fig-1.10 Development of breast



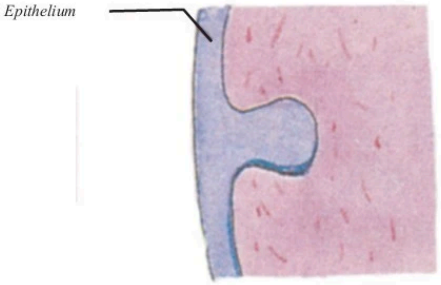
Late Fetus

Fig-1.11 Development of breast



12 weeks I.U.

Fig-1.12 Development of breast



6 weeks I.U.

Fig-1.13 Development of breast

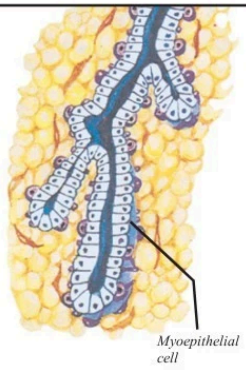


Fig-1.14 Histology of non lactating breast

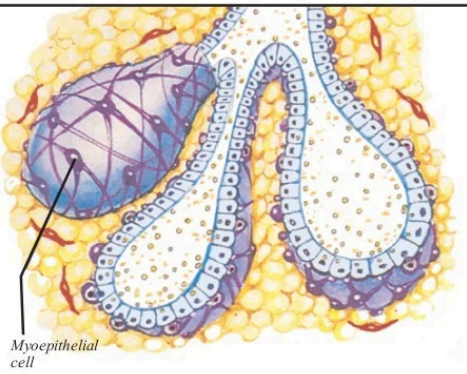


Fig-1.15 Histology of lactating breast

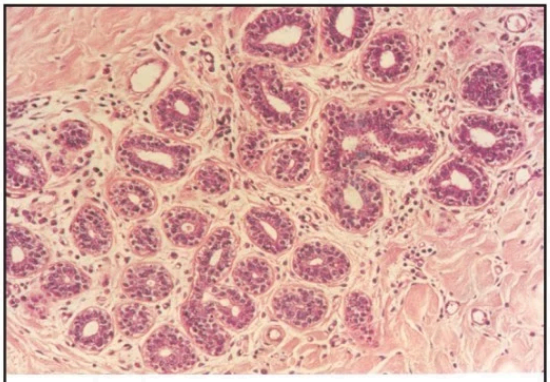


Fig-1.18 Histology of non lactating lobule

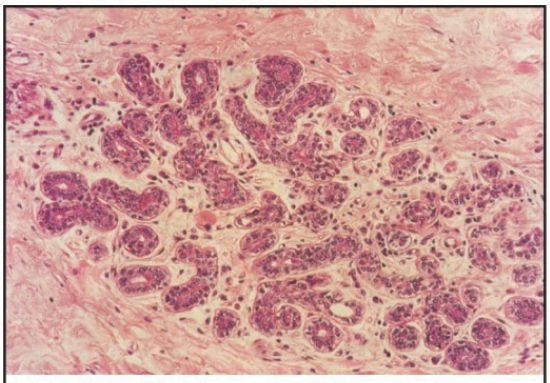


Fig-1.16 Histology of non lactating breast
Terminal duct lobular unit (TdLu)

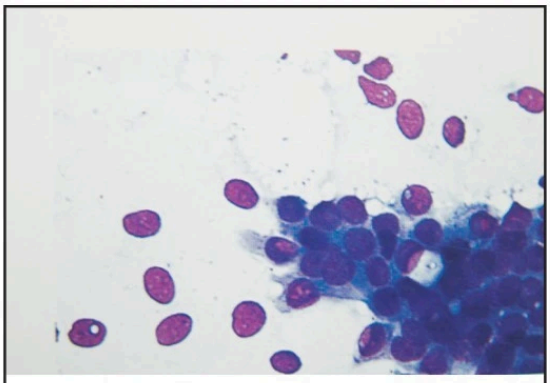


Fig-1.19 FNAC showing common benign picture

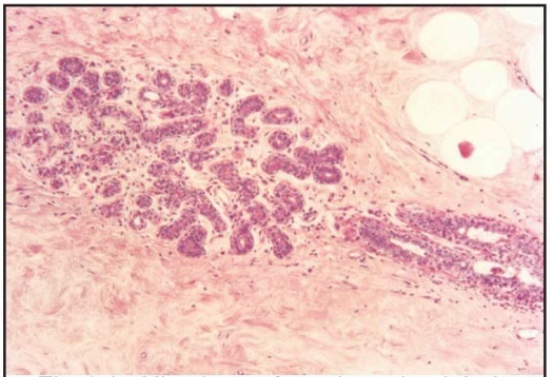


Fig-1.17 Histology of non lactating lobule
Terminal duct

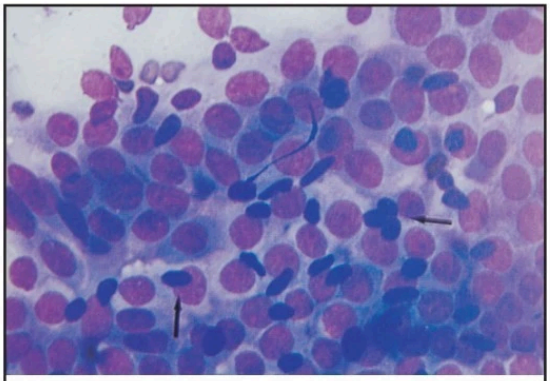


Fig-1.20 FNAC showing common benign picture

Chapter-02

Triple Assessment - 1-1 Physical Examination

Objectives

- To detect the breast problems at the earliest stage.
- To differentiate between benign and malignant breast problems.
- To assess the extent of disease (stage of disease).
- To plan effective management & follow up.
- To document the clinical data for audit.
- To counsel the patient and her attendants adequately.
- To learn the skills of examination.

TRIPLE ASSESSMENT - 1 PHYSICAL EXAMINATION

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TRIPLE ASSESSMENT

It is a combination of three modalities of assessment performed to confirm the diagnosis and status of breast disease specially carcinoma of breast. It includes following different modalities to assess the disease process;

Clinical data
(Clinical History and examination findings)

Imaging (Mammography).
Ultrasound examination (Sonomammography).
X ray Mammography (Radiomammography).
Xeromammography.
Magnetic resonance imaging (MRI mammography).

Cyto-histological examination.
(FNAC, Tru cut or CORE Biopsy or Excision Biopsy).

The diagnostic sensitivity of triple assessment ranges from 85-95%. It covers all the medico-legal aspects of the diagnosis and treatment of breast malignancy.

The reasons for breast examination training of the students is to learn to detect mass in the breast and to improve the clinical skills[2].

The objective of clinical breast examination is to differentiate normal physiological nodularity from discrete breast mass. If a discrete mass is detected, its evaluation is mandatory in all cases to exclude breast cancer.

It is guided by clinical findings, age of the patient and her personal risk status[1].

A careful clinical examination is an essential part of breast screening in order to reduce false negative results[3].

A standardized system to describe clinical breast examination (CBE) alerts physicians to an increased risk of delayed diagnosis of breast cancer[4].

PHYSICAL EXAMINATION OF BREAST

It is the first part of triple assessment. It may be the examination conducted by the doctor (clinical breast examination)

clearly understandable by the patient. The examination room provides enough comfort and privacy to avoid embarrassment to the patient. A female nurse or attendant should always be present when the examining doctor is a male. The room temperature should be comfortable. The light should be adequate and patient should be completely exposed above the umbilicus.

SPECIAL INTERVIEW

Certain information such as; age of menarche, menstrual history of patient, obstetric history, history of lactation and breast feeding, history of breast cancer and other malignancies in the family is very carefully noted. History of hormonal intake for contraception or as replacement therapy needs att-ention.

Following specific questions are asked before examination is started;

Complaints of lump, nipple discharge, pain or change in size of breast with duration.
Pain in back, shoulder or hip areas.
Menstrual cycle and its disturbances.
Age of menarche+Menopause (if elderly).
Number of pregnancies
History of lactation.
Age at first pregnancy.
Relevant family history both in first and second degree relatives.
History of contraceptive pill intake.
History of hormone replacement therapy with its duration.

ALWAYS EXAMINE BOTH BREASTS

In supine position.
In semi recumbent position.
In semi recumbent position with hands abducted (over head).
In semi recumbent patient with hand pressing over the hips.
In leaning (dependent) position.

The patient stands away from the table and rests her hands on the table leaving her breasts hang freely. All the findings are recorded on the diagram.

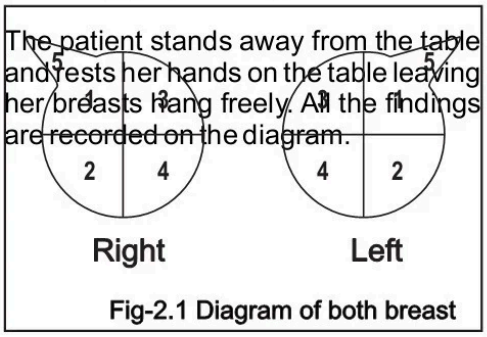

Fig-2.1 Diagram of both breast

INSPECTION

Both sides should be examined simultaneously.

NIPPLES

Look for;

Shape of the nipple.
Discharge from the nipple, its amount and color.

Fig-2.2 Sitting patient

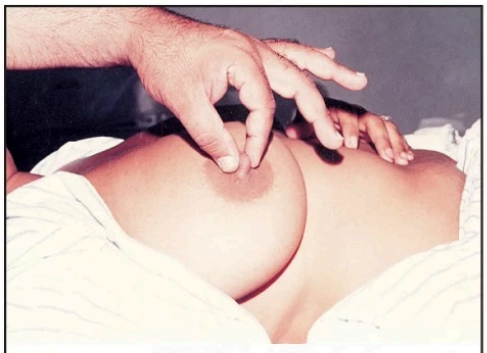

Fig-2.4 Feel the nipples

Fig-2.3 Sitting patient with hands abducted

Fig-2.5 Fixity of overlying skin

Fig-2.6 Lying patient with hands pressing against pelvis

Color of the skin.

AREOLA

Look for;
Color of the skin.
Skin pigmentation or de pigmentation.
Lumps.
Surrounding area.

BREAST PROPER

Look for;
Size of the breast.
Shape of the breast.
Color of the skin.
Puckering of skin.
Symmetry of breast.
Visible veins.
Scars.
Signs of inflammation.
Lumps.
Peau-de-orange.
Fungating Mass.
Ulceration.

PALPATION

Patient should be asked to point out the site of lesion.
Normal breast should be palpated first.
Ask about the painful area of the breast.
It should be examined at the end.

SUPERFICIAL PALPATION

Whole of the breast should be palpated with the flat of hand gently. It makes the lump or tender areas obvious.

DEEP PALPATION (PRECISE PALPATION)

The precise palpation of the lump can be performed between thumb and fingers. The palpation is performed systematically to avoid missing lump in any part of the breast.

Feel the;
Nipples.
Areola.
Breast proper.

Skin temperature is felt over and around the breast. Tenderness and point of maximum tenderness is noted.

All observations are marked on the diagram shown below in patients with breast lump.
Note the following points as well;

SITE

Exact site in relation to the quadrants of the breast should be recorded as;

Upper outer quadrant.
Lower outer quadrant.
Upper inner quadrant.
Lower inner quadrant.
Axillary tail.
Nipple and areolar lesions are noted.
Side of the breast (Right or Left) is always mentioned.

SIZE

Exact size of the lump is measured and noted in centimeters in two dimensions.

Fig-2.7 Measurement of the lump (incorrect method)

Fig-2.10 Fluctuation

Fig-2.8 Measuring the breast lump with the help of caliper

Fig-2.11 Transillumination (Examination in Dark room)

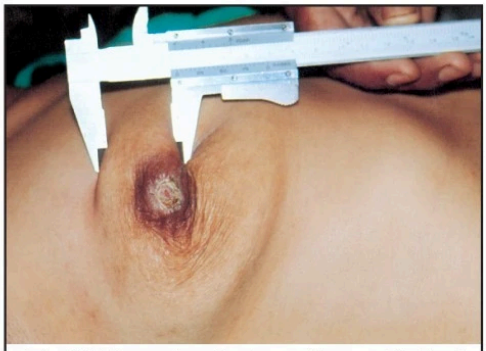

Fig-2.9 Measuring the breast lump with the help of caliper

Fig-2.12 Large size carcinoma left breast (T4)

irregular lumps. The measurement of the largest diameter of the lump is performed with the help of caliper. It is essential for the proper staging of the disease. The speed of increase in size is mentioned in the history.

SHAPE

It should be drawn in the diagram of the breast.

CONSISTENCY

The lump is palpated between thumb and the index finger and the consistency is recorded as;

Soft (similar to touch of cheek).
Cystic (similar to touch of water filled balloon).
Firm (similar to touch of tip of nose).
Hard (similar to touch of forehead).

SURFACE

It is felt and recorded whether smooth or nodular.

MARGINS

Margins of the lump are felt. These can be;

Diffuse (Not clearly demarcated).
Clearly demarcated.
Regular.
Irregular.

MOBILITY / FIXITY

Fixity or mobility in relation to overlying skin or underlying structures is examined. The skin is lifted up between thumb and the index finger. The skin is rolled over the lump in all directions.
It clearly differentiates the fixity or mobility of the skin. The lumps present in the skin become obvious as well.

The patient is asked to push against both iliac crests. This puts the pectoralis major muscles into contraction on both sides.

The lump is moved over the fixed and contracted (Hard) pectoralis major muscles in all directions. It clearly shows the freely mobile or fixed nature of the lump.

FLUCTUATION

It is tested carefully. The lump is fixed between two fingers of one hand and it is pressed with the index finger of the opposite hand. The lift up of the stationary finger is felt. The fluctuation is tested in two planes at right angle to each other.

It is positive in cystic (fluid filled) lesions.

TRANSILLUMINATION

It is performed in the dark room with a powerful pencil torch. Fluid filled lumps (Cysts) become obvious (red glowing areas) indicating positive transillumination test.

OTHER FEATURES OF EXAMINATION

Jaundice, pallor and edema especially of upper limbs is looked for and noted. Complete examination of liver, lungs and spine is performed to search for distant metastasis.

CLINICAL STAGING OF THE CARCINOMA BREAST(TNM)

T TUMOR
N LYMPH GLANDS
M METASTASIS

(T) STAGES

T-x
Primary tumor cannot be assessed.
(Post operative patients who were not staged initially).

T-is
Carcinoma in situ. Incidental finding showing presence of malignant cells without invasion of basement membrane.

T-0
No palpable primary tumor.
It is an incidental finding.

T-1
Tumor size 2 cm or less.
No fixity.
No nipple retraction.

T-2
Tumor size 2-5 cm.

T-3
Tumor size 5-10 cm.

T-4
Tumor size more than 10 cm.
Any size with infiltration or ulceration of the skin.
Tumor fixed to the chest wall.
Peau-de-orange appearance of the skin.

(N) STAGES

N-x
Axillary node cannot be assessed.

N-0
No palpable axillary lymph glands.

N-1
Palpable but mobile ipsilateral axillary lymph glands.

N-2
Fixed ipsilateral axillary lymph glands.

N-3
Palpable supra clavicular lymph glands mobile or fixed.
Edema of the arm.
Involvement of ipsilateral internal mammary glands.

(M) STAGES

M-0
No metastasis.

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axilla and supra clavicular lymph glands. Other distant metastasis.

STAGE I

(T0, T1,N0, M0)
This includes growths confined to the breast.

Tumor less than 2 cm diameter in size.
No nodal involvement.
No distant metastasis.

The tumor should not be adherent to the pectoral muscles or chest wall.

STAGE II

(T0, T1 OR T2 and N1, M0)
Tumor size less than 5 cm in diameter but there are affected mobile lymph glands in the axilla of the same side.

Tumor 5 cms size without lymph node involvement. No distant metastasis.

False negative results of clinical examination are about 25-30%.

STAGE III

(T0, T1, T2, T3, T4, N2 and M0)
All breast cancers of any size. Skin involvement or peau-de-orange present in larger areas than the tumor itself but these are limited to the breast. Tumor fixed to pectoral muscles but not to the chest wall.

Axillary lymph nodes, internal mammary node and Supra clavicular nodes are involved. Edema of the arm may be present.

STAGE IV

(Any T or any N with M1)
Skin involvement extending outside the breast. Distant metastasis either lymph borne or blood borne. Involvement of opposite breast.

The patient is covered and allowed to change at the end of clinical examination. The examining doctor interacts with the patient very professionally.

COUNSELING

The patient is informed about the disease status as assessed clinically.

Plan of investigations and possible modes of treatment are informed and necessary documenta-tion and appointments are made and recorded. Whole of this information is also sent to the referring doctor.

Then the examining doctor leaves the room after leaving a satisfied patient.

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CHECK LIST

1. Introduction to the patient.
2. Special interview.
3. Exposure and position.
4. Inspection.
5. Palpation.
6. Examination of axilla.
7. Staging.
8. Covering the patient.
9. Counseling.
10. Follow up appointment.
11. Letter to the referring doctor.

Chapter-03

Triple Assessment - 1-2 Self Examination

Objectives

- To be aware of the problems of breast.
- To assess the consistency of one's own breast.
- To assess any change in breast at the earliest stage.
- To be able to seek expert medical help in time.
- To learn the skills of examination.

TRIPLE ASSESSMENT - 1 BREAST SELF EXAMINATION

Shuja Tahir, FRCS, FCPS

It is also first part of triple assessment for breast diseases.

The female patients are advised to conduct their breast examination once a month. It is not performed more often unless asked by the doctor.

SETTING

The patient should conduct self examination of breast in a room with comfortable environment and privacy. It may also be conducted in the bath room with availability of mirror.

The patient should remove her shirt, vest and Bra' to see the breasts, chest, neck, arms and both axillae clearly.

The patient should follow following instructions;

Breast self examination (BSE) takes just a few minutes and the patient only needs to do it once a month.

If the patient is menstruating, she should perform BSE 7 to 10 days after the first day of period, when the breasts are least tender.

If the patient no longer menstruates, she is to choose the same day of each month to do BSE.

The goal of BSE is to become acquainted with how the breasts normally look and feel. Patient's knowledge of the breast texture and appearance improves as she performs BSE. This knowledge helps her to identify a change more quickly and report it to her doctor.

INSPECTION

Use a mirror.
First, stand in front of a mirror, keeping your arms relaxed at your sides.

Notice the shape and size of your breasts. Compare both breasts. It is not unusual for one to be larger than the other.

Next look at your skin. Take note of the texture and color changes. Put your hands on hips. Look at the breasts with your arms in different positions.

Some of the changes patient should watch for;

further evaluation.

PALPATION

As you do this part of the examination, remember that some lumpiness is normal for many women. Self examination helps you become familiar with the normal texture of your breast tissue.

To examine your right breast, lie on your back.

Place a pillow or a folded towel under your right shoulder. Put your right arm out, with your elbow at a 90 degree angle.

This position flattens and makes it easier to examine. Feel whole of your breast with your left hand.

Use the padded area of your fingers and not the tips. Use the pads of three or four fingers of your left hand to examine your right breast. Move your fingers in very small circles.

For each small circle, change the amount of pressure so for you can feel all levels of your breast tissue. Don't lift your fingers from your breast as you move them, you might miss something that way. You may use lotion to make it easier for your fingers to slide over your skin.

Make a pattern of vertical strips examination and cover the self examined area in vertical strips. Start in your armpit and move down to just below your breast. Now move your fingers over just the width of one finger and move up again. Continue this up and down pattern until you have covered the entire breast self examination, from your collar bone to just below your breast.

Relax your arm and examine your armpit. Some parts of your breast go up into your armpit. Examine this area again with your arm relaxed at your side. It will feel a little different in this position. Check for fluid coming from your nipple. Gently squeeze your nipple. Clear or milky fluid coming from the nipple is more common than blood stained fluid. All nipple discharges should be checked by your doctor.

Repeat the same steps using your right hand to examine your left breast. You may conduct the above examination steps while in the shower or bath (standing or lying).

What to do if you find a lump?

Do not panic;
Eighty percent of lumps found are not cancerous. See your doctor. Remember Breast cancer can develop at any age, but your risk increases as you grow older.

CHECK LIST

1. Exposure.
2. Inspection.
3. Palpation.
4. Squeezing the nipples for discharge.
5. Feeling the axilla.
6. Cover yourself.
7. Report to the doctor.

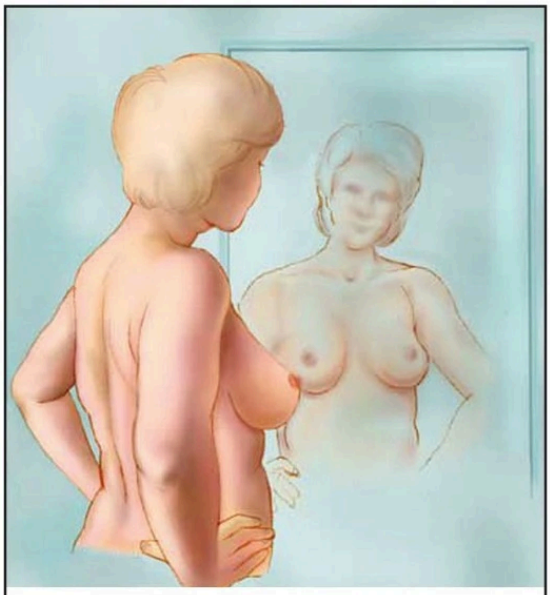


Fig-3.1 Stand in front of a mirror normally

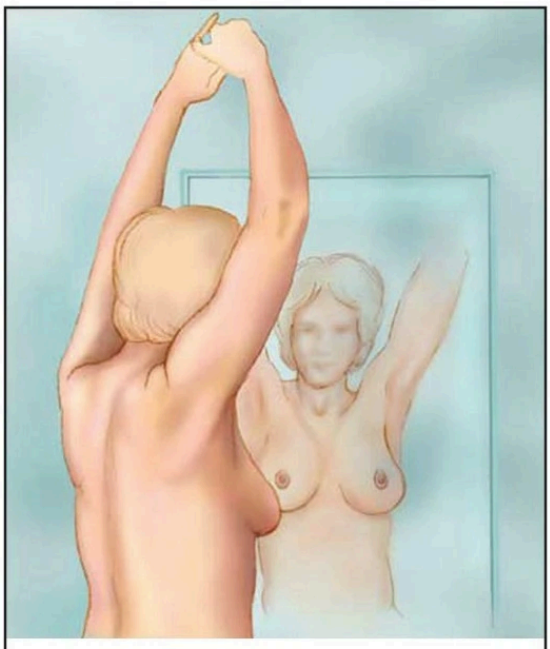


Fig-3.2 Standing in front of mirror with arms abducted

Fig-3.3 Feeling the breast while in shower

Fig-3.4 Feeling the breast while in bed

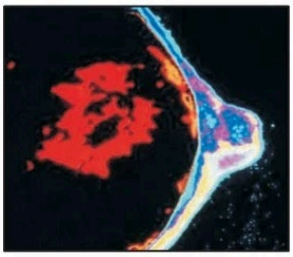
Chapter-04

Triple Assessment - 2 Imaging

Radio Mammography
Sonographic Mammography
Magnetic Imaging Mammography

Objectives

- To accurately diagnose various benign and malignant lesions of the breast.
- To detect the malignancy at earliest in a female population.
- To evaluate and monitor the high risk females for malignancy of breast.
- To assist in evaluation and management of symptomatic breast problems.
- To detect unsuspected lesions in same or opposite breast.



TRIPLE ASSESSMENT - 2 IMAGING (MAMMOGRAPHY)

Shuja Tahir, FRCS, FCPS

Mammography is visualization of the soft tissue structure of the breast using various techniques.

It includes imaging of the breast using different modalities given below;

Radiological examination of the breast using dedicated machines.
(Radiomammography, Xero-mammography)
Ultrasound examination of breast (Sonomammography)
Magnetic resonance imaging of breast (MRI mammography)

MAMMOGRAPHY

Mammography is the radiological visualization of the soft tissue structure and architecture of the breast at various stages of its life. It is used to diagnose various breast diseases. It is also called screen film mammography. Both breasts are always examined and compared before this investigation is performed. It can be performed on symptomatic and asymptomatic patients.

HISTORY & DEVELOPMENTS IN MAMMOGRAPHY

1913 (Albert Salomon);
A surgeon, reported the usefulness of radiography of mastectomy specimens to reveal the spread of tumor to axillary lymph nodes.

1930 (Stafford L. Warren);
He reported the use of stereoscopic technique for in vivo mammography.

1940 (Raoul Leborgne);
He reported the presence of radiologically visible micro calcifications in breast cancer. He was one of the first to recognize the importance of breast compression for improving the image quality.

He emphasized the radiographic difference between benign and malignant calcifications.

1960 (Robert L. Egan);
He described a high mA-low kV mammographic technique.

1963 (Gerald Dodd);
He became the first person to perform the needle localization of non palpable,

1965 (Charles Gros (France));
He developed the first "dedicated" mammography x-ray unit.

1970 (Dupont, Eastman Kodak company);
The Dupont company produced the first marketed dedicated screen-film mammography system. The Eastman Kodak company followed with its own high detail screen-film combination and introduced the vacuum cassette for mammography.

1971 (Stephen Gallager & Martin);
They published their concept of "minimal" breast cancer which they defined as a highly curable lesion. They were the first to recognize a focal "new density" in serial mammograms as a sign of early carcinoma.

1974 (Myron Moskowitz and his colleagues);
They presented the early results of screening.

1976 (Howard Frank, Feris Hall & Michael Steer);
They described a needle hookwire assembly for preoperative localization of non-palpable lesions found at mammography.

1977 (Edward A. Sickles, Kunio Doi & Harry K. Genant);
They published the results of their investigation of magnification mammography.

PHYSIOLOGICAL BASIS FOR MAMMOGRAPHY

The breast tissue (mammary gland) is collection of glands surrounded by

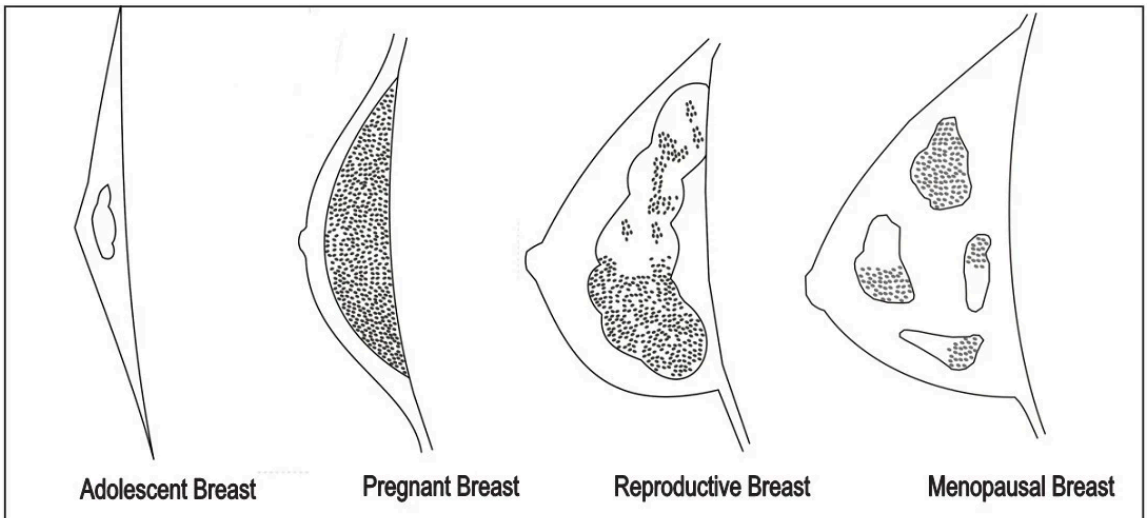


Fig-4.1 Drawing of mammary gland showing variation and distribution of radiographic density related to normal life cycle

It is the radiologic differentiating ability of fat which helps in the diagnosis, differentiation and study of the internal structure of the breast tissue.

The fat content is present between the glands, lobules, lobes, sub-mammary space and sub cutaneous space. It is usually not present under the nipple and is minimally present under the areola.

The breast has dense connective tissue and normally developed mammary glands at puberty. It shows dense homogenous picture on mammography.

The amount of fat present in and around the breast varies from person to person. The increase in glandular content

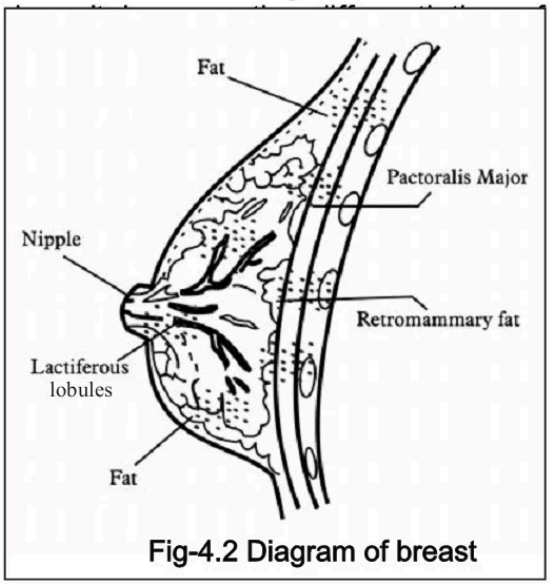


Fig-4.2 Diagram of breast

The glands and ducts hypertrophy during pregnancy, but these are again of water density. The mammographic picture remains homogeneously dense and becomes extremely radio-opaque.

The glands and the ducts involute after delivery and lactation. The parenchymal involution is followed by some degree of fat deposition. It gives good radiographic differentiation to breast tissue.

RISKS OF MAMMOGRAPHY

There is always a slight risk of damage to cells or tissue from being exposed to any radiation, including the low levels of radiation used for this test. However, if this test is really needed, the risk of damage from the x-rays is very low compared with the potential benefits of the test.

Newer x-ray techniques have dramatically reduced radiation exposure during mammography. The dose of radiation used for a mammogram is similar to that used for a dental x-ray.

NORMAL MAMMOGRAM

Breast shadow looks normal. No unusual growth, lumps or other types of abnormal tissue are seen. The glands that produce milk for breast feeding and the tubes (ducts) through which milk flows appear normal.

Calcifications are most often non cancerous. Tiny calcifications (micro-calcifications) often occur in areas where cells are growing very rapidly (such as in a cancerous tumor). Larger calcifications (macro-calcifications) are usually normal in women over the age of 50.

A mammogram is not usually performed for a pregnant woman, because the radiation could damage her developing fetus. If a mammogram is absolutely necessary, a lead apron is placed over the woman's abdomen.

A mammogram is usually not performed for a woman who is breast feeding, because breast that contains milk shadow, homogenous opacities and diseased area cannot be differentiated.

Deodorants, perfumes, powders or ointments on the breast may interfere with the x ray pictures.

Breast implants or scar tissue from previous breast surgery may make a mammogram more difficult to interpret due to radiographic abnormal shadows.

PREPARATION FOR MAMMOGRAPHY

No special preparation is required other than having the patient dressed in an open front gown for adequate exposure of the breast during mammographic examination. A female attendant must accompany the patient throughout the examination.

The patient is counselled about the procedure briefly and precisely. A careful physical examination is conducted and all findings are noted. Scars, lump, induration, eczematous lesion, ulcers and pigmentation is drawn on the diagram. No feature is missed, no matter how trivial. Both breasts are examined and compared, findings are recorded for future reference.

INDICATIONS FOR MAMMOGRAPHY

To screen asymptomatic women.
To assist in evaluation of symptomatic breasts for management decisions.
To detect the unsuspected lesion in same and opposite breasts having palpable mass.
To serve as baseline for comparison with subsequent mammography for accurate and early detection.
To evaluate breast status before starting Hormone Replacement Therapy (HRT) in menopausal women.

MAMMOGRAPHIC EXAMINATION

The patient sits or stands in front of mammography machine and puts her breast over the movable compression device.

The compression device has two plates. One of these is mobile and x-rays can pass through these. The breast is compressed between these

The breast of the patient is compressed gently and evenly between two plates of the mammographic equipment. It helps in uniform differentiation of the internal structure of the breast.

Compression is one of the most important aspect of mammography. It helps to achieve;

Good picture resolution as it separates the overlapping structures.
A sharp image due to immobilization.
Exposure under automatic control.
Uniform and smooth resolution.
Use of minimum irradiation.

Both breasts are exposed in two or more views separately. The mammographic examination is usually satisfactory in two dimensions;

Cranio-caudal[1,2,3]
Medio-lateral or oblique medio-lateral

Oblique views and cone views may be required in highly suspicious lesions for better resolution and detection.

Each breast is examined separately. Maximum breast tissue is compressed to avoid missing peripheral lesions.
Dedicated mammographic machines have been developed which help to achieve better resolution and use very low dose of x-ray irradiation.

Structures upto 1 mm size can be picked up by these machines and patient is exposed to minimum x-ray irradiation. These machines result in less than 2 rads exposure per examination.

The machines use low kilovolt peak x-ray technique which enhances the radiographic contrast of fat and water content of the breast and give best radiographic view of the inside of the breast.

The screen film mammogram gives maximum information. It can be used to put markers at the suspected lesions to help the surgeon during surgery.

Sometimes radio-opaque dye or methylene blue is infiltrated in the area of mammographically suspected lesion to help the surgeon while taking biopsy. Staining due to methylene blue may not be very helpful while performing fine needle aspiration cytology or tru-cut needle biopsy. Guide wire can also be inserted in the lesion mammographically.

The films are examined very carefully keeping in mind the age of the patient and status of the breast. An amplifying lens is used for proper examination and interpretation.

A normal mammogram does not guarantee that breast cancer is not present.

Most abnormalities found during mammography are not cancer. However, many women who have

detect breast cancer.

MRI can detect suspicious areas in the breasts, but many suspicious areas turn out to be normal (false positive results). MRI is useful when a diagnosis is difficult to make due to previous surgery using other methods. MRI is much more expensive than x-ray mammography and is not used very often to examine the breasts.

Nuclear scanning tests use a radioactive tracer(called a radionucilide) that is injected into a vein. The tracer travels through the blood vessels and can accumulate in many types of tumors. The location of the tracer is detected by gamma camera that scans the body for areas where the tracer has accumulated. Nuclear scanning tests are useful when a diagnosis is difficult to make using other methods.

Although breast cancer can occur in men, it is rare. About 99% of all breast cancer is found in women.

ADVANCEMENTS IN MAMMOGRAPHY

XEROMAMMOGRAPHY

Xeromammography is a specialized radiological processing system using dry electrophotographic technique. A charged aluminium plate coated with selenium powder is used instead of traditional screen film in this investigation. The image is then transferred to the photographic paper plate. Whole of this process is performed by an automatic processor machine.

The xeromammographic image gives less overall information than radiological mammogram. It definitely demonstrates the important features and resolution is sufficient to show micro calcification.

DIGITAL MAMMOGRAPHY

It is a mammographic imaging system that acquires mammograms directly in digital form. It has the ability to display finest details and improve the performance of mammography.

It allows to view different parts of the breast without taking additional images. Image from digital mammography can be magnified and stored electro-nically more easily than images from standard mammography. Digital mammography is not yet widely available.

COMPUTER AIDED DETECTION & DIAGNOSIS (CAD)

It is a type of digital mammography which can facilitate computer aided detection and diagnosis which is otherwise not easily possible. It helps to detect lesions which might be missed by the examiner. It, in fact increases the detection sensitivity. It can further help in the correct diagnosis due to availability of large data bank for comparison and correct diagnosis. It is

images are removed and relevant structures are preserved and interpreted.

DIAGNOSIS

The mammogram may shows normal breast architecture according to the age of the patient or may show benign lesions such as;

Fibro adenoma.
Cystic lesions.

The mammography may diagnose malignant lesions such as;

Non invasive carcinoma of breast
DCIS
LCIS
Invasive carcinoma of breast

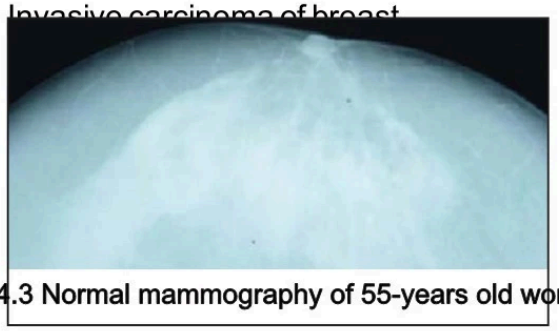


Fig-4.3 Normal mammography of 55-years old women

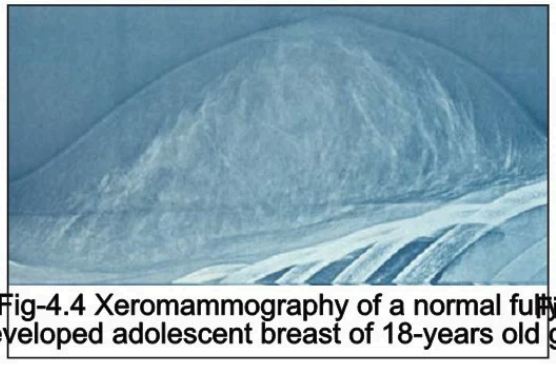


Fig-4.4 Xeromammography of a normal fully developed adolescent breast of 18-years old girl

BENIGN LESIONS

Benign calcifications are larger and uniform in size and shape.

These may be multiple and bilateral. Coarse and peripheral calcification is

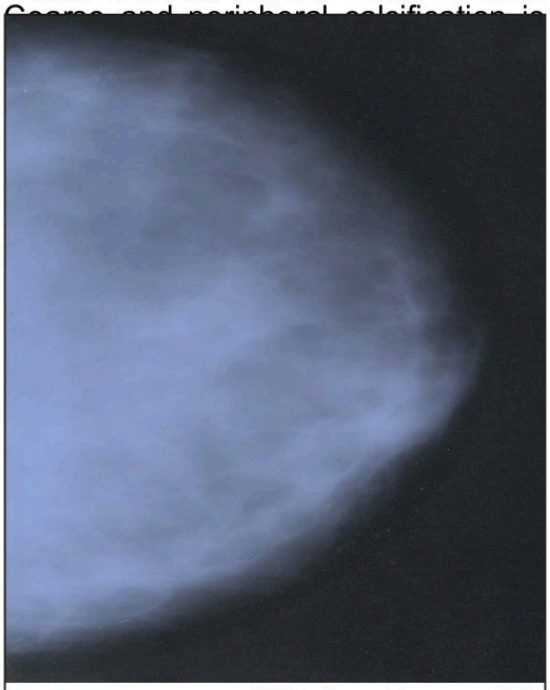


Fig-4.5 Mammography of normal breast of 15-years old gir

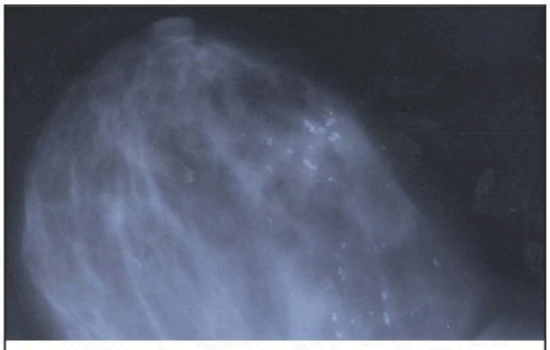


Fig-4.6 Mammography of breast showing calcification of lactiferous ducts (DCIS?)

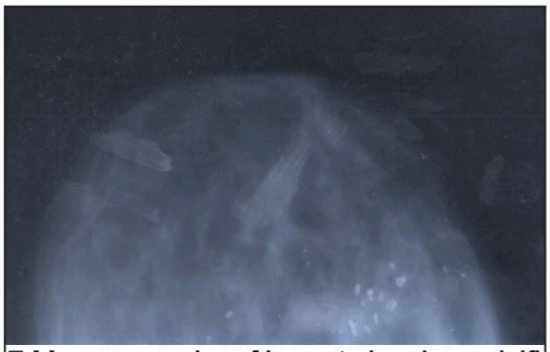


Fig-4.7 Mammography of breast showing calcification of lactiferous ducts (DCIS?)

Cyst appears as a well circumscribed mass. Ultrasound scanning helps to differentiate it from a solid lesion. It appears as a compressible mass with smooth back wall and no internal echoes and hypo-echoic pattern on ultrasound examination of breast.

BREAST ABSCESS

The clinical picture is usually suggestive of diagnosis. Radio mammography is painful and less helpful. The diagnosis is usually clinically obvious. Ultrasound examination is much fruitful and offers excellent interpretation.

Sono-mammography is more acceptable to the patient and helpful in diagnosis by showing hypo echoic area of fluid or pus collection.

CARCINOMA OF BREAST

It shows as a spiculated mass. The irregular margins are very clearly seen. It can be easily diagnosed.

Sometimes well circumscribed mass can be seen and irregular margins may not be clear. (Medullary carcinoma) The masses may be multiple.

Sometimes the mass may not be seen

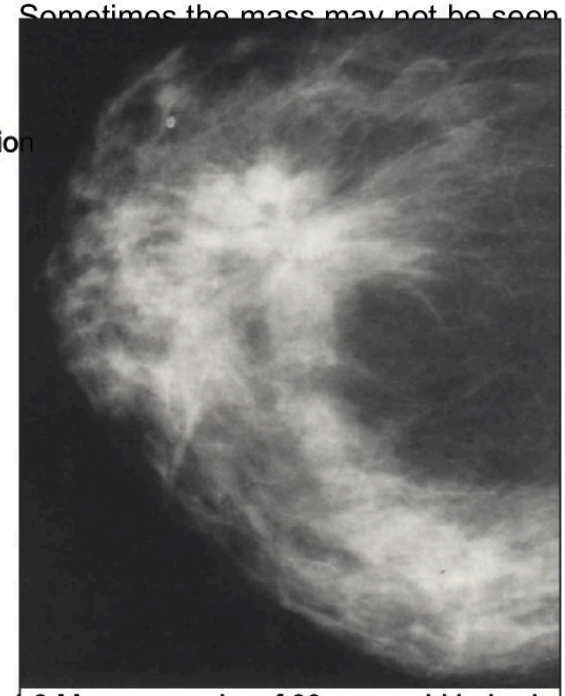


Fig-4.8 Mammography of 60 years old lady showing invasive ductal carcinoma

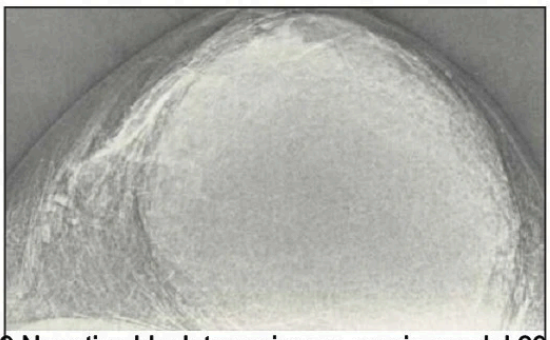


Fig-4.9 Negative black toner image cranio caudal 29 years old women with history of injury. (Angiosarcoma)

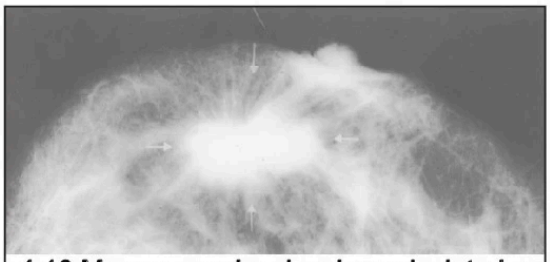


Fig-4.10 Mammography showing spiculated mass behind the nipple (carcinoma of breast)

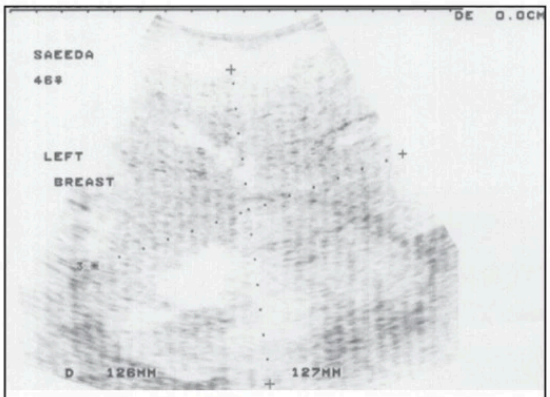


Fig-4.11 Giant fibroadenoma of breast

SONO MAMMOGRAPHY

ULTRASOUND SCAN OF THE BREAST

It is ultrasound examination of the breast. Ultrasound is helpful in differentiating between solid and cystic lesions of breast with a specificity of almost 100%. Ultrasound is most helpful initial imaging study[1].

It has a sensitivity of 75% and positive predictive value of 90% in the diagnosis of breast cancer[12].

Ultrasonic mammography is a completely non invasive investigation. It can be performed to confirm the diagnosis of breast abscess which is very painful on compression during radio mammography.

It is economical and patient friendly. It is performed with special probe on 7.5 or 10 MHTZ. It helps to pick up cystic and fluid containing breast lesion with almost 100% certainty.

Sono mammography is practically useful in younger women below 35

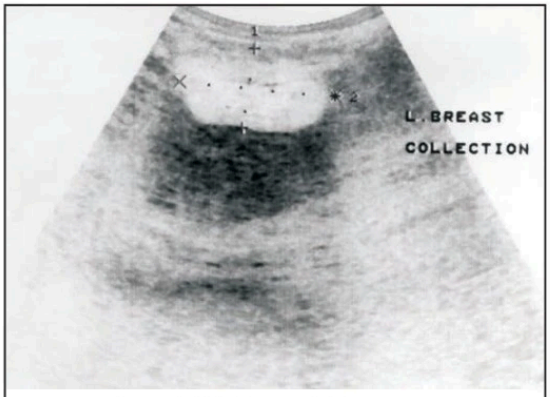


Fig-4.12 Breast Abscess

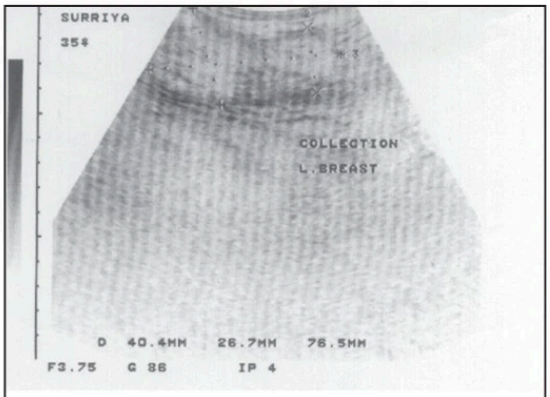


Fig-4.13 Collection of fluid (breast abscess)

the finer details of the superficial and subcutaneous tissues. 7.5-10 MHz probe is used for good resolution.

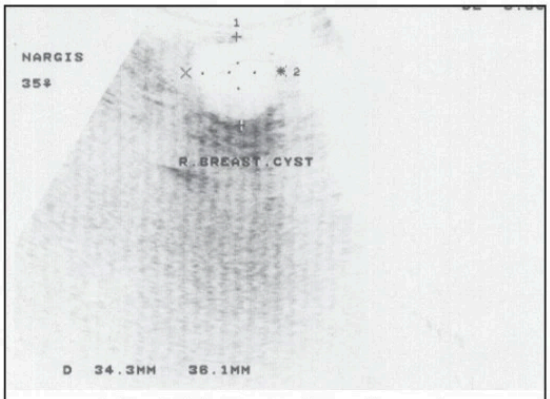


Fig-4.14 Cyst of the breast

The cystic lesions can be diagnosed with certainity. These appear as well circumcised, with a smooth wall and hypoechoic center (posterior enhancement is also seen. Ultrasound guided trucut needle biopsy yields nearly 100% accurate results and can in fact replace the excisional biopsy[4].

It is useful for guided aspiration of cysts, needle biopsy of solid tissue lesions and fine needle aspiration cytology. Its resolution is less superior for solid lesions when compared with radio mammo-graphy.
As many as 50% of non palpable breast lesions can be picked up by ultrasound scan. Intra operative ultrasound can be used to direct the excision while improving margin negativity. Ultrasound guided breast biopsy can facilitate excision of such masses[9].

Ultrasound examination of breast can be interpreted as;

R1 Normal/ benign
R2 Discrete / benign
R3 Intermediate
R4 Suspicious
R5 Malignant

MAGNETIC RESONANCE IMAGING OF BREAST (MRI MAMMOGRAPHY)

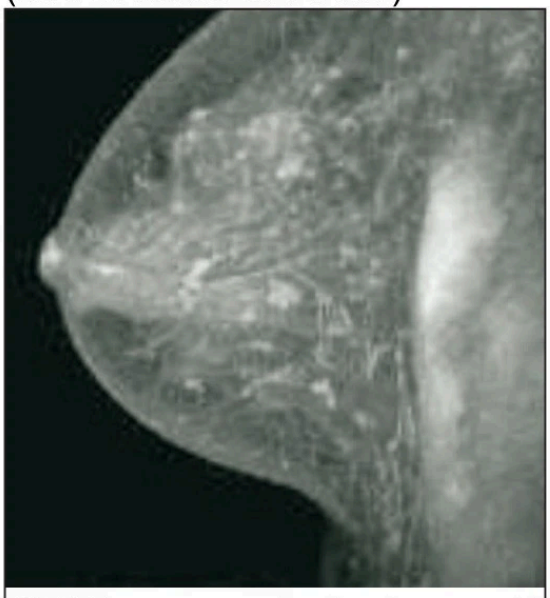


Fig-4.15 MRI mammography showing normal breast

It is non invasive. It has great value in detection of vertebral body metastasis and musculo-skeletal pathology related

cases, it is used to detect the breast lesions with improved specificity and sensitivity[5].

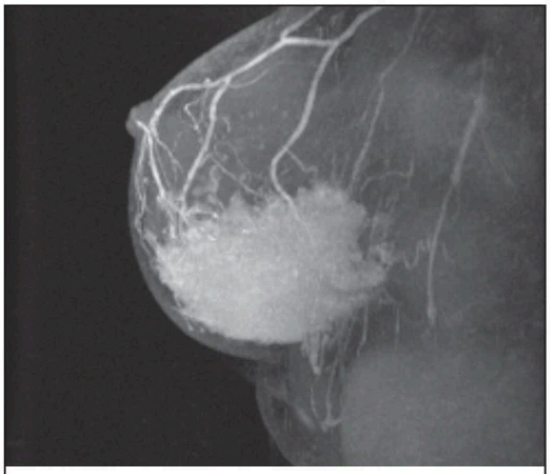


Fig-4.16 MRI mammography of patient with nipple discharge

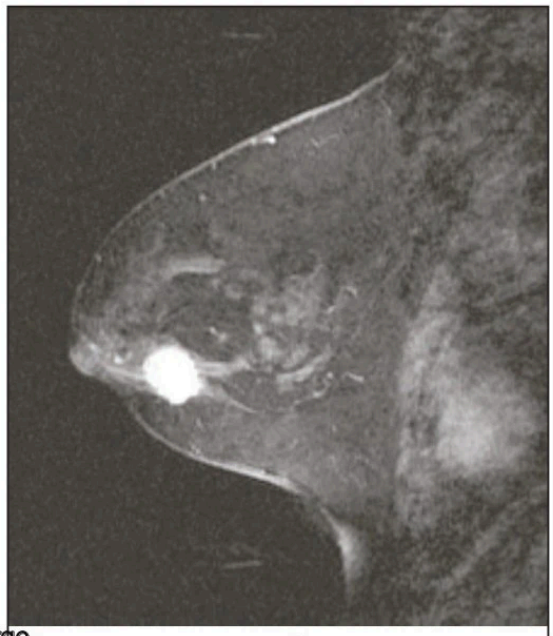


Fig-4.18 MRI mammography (Invasive carcinoma breast)

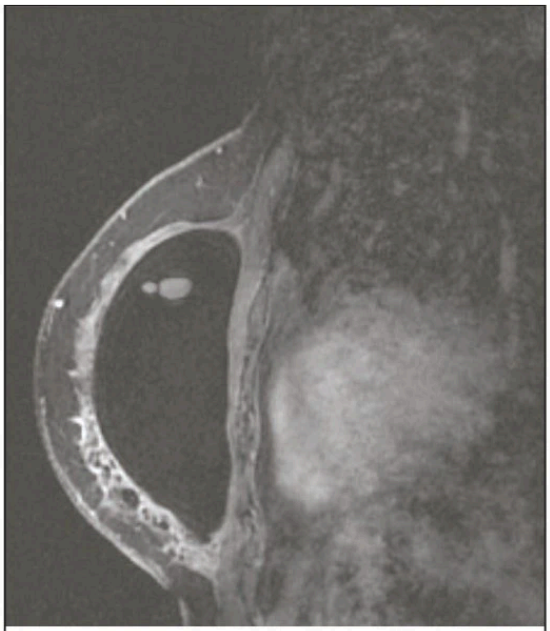


Fig-4.17 MRI mammography showing bubble in implant

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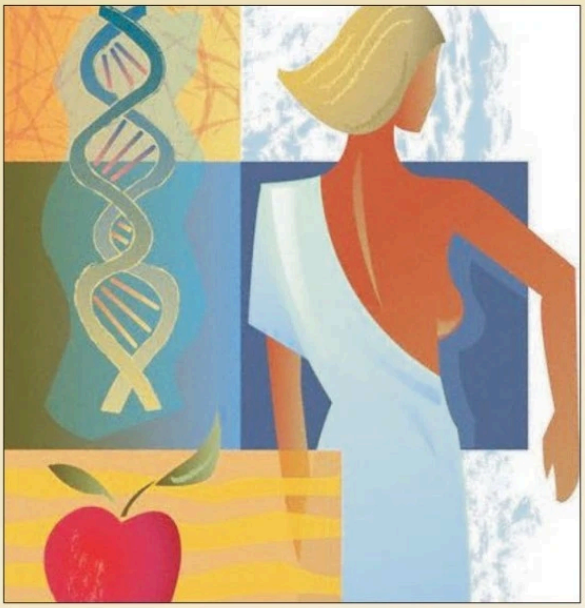
Chapter-05

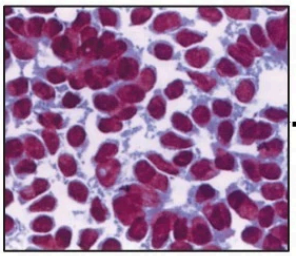
Triple Assessment - 3
Cyto Histological Examination



FNAC
Core Biopsy (Tru Cut Needle)
Excision Biopsy

Objectives

- To confirm the diagnosis.
- To differentiate between benign and malignant breast problems.
- To assess the extent of disease (stage of disease).
- To plan effective management & follow up.
- To document the data for audit.
- To counsel the patient and her attendants adequately.
- To learn the skills of examination.



TRIPLE ASSESSMENT - 3 TO HISTOLOGICAL EXAMINATION

Shuja Tahir, FRCS, FCPS

Cyto histological examination is the microscopic examination of cells and tissue after appropriate preparation and staining.

It includes following tests;

FNAC.
Trucut needle biopsy.
Excision biopsy.

All these tests are used to confirm the diagnosis.

FINE NEEDLE ASPIRATION

Fine needle aspiration (FNA) of a palpable cyst is both diagnostic and therapeutic.

It is aspiration of cyst and cytological examination of the cyst fluid.

Normally the aspirated fluid of cyst is clear, yellow or green but it may be blood stained.

The advantage and the pleasure, this procedure provides to the patient is great as a women who seeks medical advice thinking about cancer breast finds herself without any lump in the breast in few moments after aspiration of the cyst and gets confirmed diagnosis within hours.

These patients must be followed up at monthly intervals.

The lump must be either cytologically examined or excised and sent for histological examination in case following features are encountered;

- If aspirated fluid is frankly blood stained.
- If the lump does not completely disappear on emptying the cyst.
- The cyst refills rapidly or recurs after two aspirations.
- Aspiration fails.

FINE NEEDLE ASPIRATION CYTOLOGY

FNAC is the first line investigation of choice for both superficial and deep lesions of the breast and other body tissues. It is an essential part of triple assessment for diagnosis in palpable breast lumps.

It can achieve excellent results if efforts

suspicion valuable in the diagnosis of inflammatory, infectious and degenerative conditions.

Intra-operative cytology is valuable alternative or complement to frozen section examination.

FNAC is the last part of (third) Triple assessment of breast lesions. Main objective of FNAC is to confirm carcinoma preoperatively and avoid unnecessary surgery in specific benign conditions.Cytology results can be available within 30-60 minutes.

These are described on a five point scale;

C1 Inadequate (cellular sample).
C2 Benign.
C3 Atypical (Probably benign).
C4 Suspicious of malignancy.
C5 Malignant.

FNAC may be repeated immediately in C1 lesions or immediate core biopsy sample may be taken. FNAC is not helpful if repeated few days later.

Patients who are pregnant, lactating or on Hormonal Replacement Therapy (HRT) may have altered cellular morphology and patients with previous radiation also show cellular alterations.

FNAC is not a substitute for tissue biopsy.

INDICATIONS

Fine Needle Aspiration Cytology is used for;

- Diagnosis of simple cysts.
- Investigation of suspected recurrence or metastasis in cases of previously diagnosed cancer.
- Confirmation of inoperable or locally advanced cancer.
- Preoperative confirmation of clinically suspected cancer.
- Investigation of palpable lump (clinically benign or malignant).
- Complementing mammography in the screening for carcinoma.
- Obtaining tumor cells for special analysis and research, e.g. hormone receptor studies, DNA analysis, immunohistochemistry, cell kinetics and molecular studies. It is also used for nuclear morphometry, ploidy pattern, microspectro-photometry, flow cytometry and video image analysis.
- Indicating prognosis through cytological grading which correlates with nuclear and histological grade.
- The cytological grading has a limited independent value as prognostic indicator.
- Immuno-histochemical quantification of Estrogen & Progesterone receptors which is an important development in breast cancer management.
- Monitoring of the breast cancer

- Low risk of complications.
- No extra staff required.
- Suitable for very ill and debilitated patients.
- Can be performed any where and in any department.
- No difficulties in re-biopsy due to presence of haematoma or other complications.
- Immediate diagnosis relieves anxiety of patient and saves time.
- Advance planning of definitive treatment is possible.
- Staging and metastatic work up can be initiated in malignancies.
- Benign conditions are diagnosed and mutilating surgery may be avoided.
- Hospital facilities are economically used.
- Frozen section diagnosis is
- reduced.

It is an easy and simple method to collect the specimen. It does not require any special preparation. It is a very convenient and minimally invasive method.

The results are extremely satisfactory in good hands. The cytological examination must be performed in the solid lesions. False results may be encountered occasionally. Most of the studies have confirmed correct results in about 96% of the tests which is very significant.

An overall correct diagnosis can be made in 88.67% of cases by FNAC[2].

The exact cytological diagnosis is available before definitive surgery is planned.

The immunocytochemical examination of the aspirate is performed. It helps to differentiate various conditions of the breast.
The benign lesion shows following features on cytological examination;

It demonstrates uniform groups of ductal cells, stromal fragments and many stripped bipolar nuclei.

The ultra structural examination demonstrates ductal cells with surrounding myoepithelial cells resting on a delicate basal lamina with surrounding bundles of collagen in the interstitial space[3].

The time old belief that carcinoma will spread along the needle puncture has been proved to be incorrect.

The only risk is of missing the early carcinoma associated with the cyst. This danger can be minimized by proper follow up and biopsy examination of suspicious cases.

COMPLICATIONS

- Usually uncommon.
- Major haematomas are rare.
- Pneumothorax is rare but possible in thin patients.

piece of tissue which achieves good histological diagnosis.

False positive results are less common than with other similar procedures.

It has ability to give an unequivocal diagnosis of invasion and a more definitive diagnosis of benign lesions.

PREPARATION AND PROCEDURE

No special preparation is required. It can be performed as an outpatient procedure. Tru-cut needle is required.

Skin disinfectant solution such as tincture of iodine, betadine, Povidone, Chlorhexidene or Savalon may be used to clean the skin over and around the lump to the biopsied.

Few milliliters of local anaesthetic (2% xylocaine) is infiltrated in the skin over the lesion.

The lesion is fixed between two fingers of the left hand and correct size tru-cut needle is pushed into the lesion when it is closed and the obturator is in the needle. When the needle has just entered into the lump to be biopsied, the obturator is pushed ahead into the whole length of the lump.

The needle is closed over its obturator by pushing it forwards and whole of the needle is pulled out keeping it closed.

The needle is opened and the piece (core) of lesion (lump) is removed from the obturator and is fixed in formaldehyde solution. The specimen is sent for histo-pathological examination.
A number of specimens can be taken from different parts of the lesion and examined histopathologically for more accurate diagnosis.

Early diagnosis can be made with certainty and definitive surgical procedure can be planned before surgery is under taken.

Hospitalization is not required as it is an outpatient procedure.

It is relatively economical in terms of money, time, patient compliance, hospitalization and surgeon's efforts. It avoids complications of open surgery and general anaesthesia.

Tru-cut needle biopsy under ultrasound control achieves even better results.

In smaller lesions, the actual lesion may be missed and examination may be inconclusive.

Haematoma and bruising after biopsy may be experienced.

It has in fact replaced frozen section biopsy and minimized the use of excision biopsy.

It is a very satisfactory substitute for surgical biopsy. Automated core needle

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The excision of the whole lump with 2-3 cm adjoining fat and healthy breast tissue all around the lump is performed.

FROZEN SECTION BIOPSY

Frozen section biopsy was very popular previously. Still many surgeons prefer it. The patient is kept under anaesthesia. The suspicious tissue is excised and sent to the laboratory. The frozen section is prepared for histopathological examination. The biopsy report is received on telephone as early as possible usually within 30-60 minutes. Further procedure is carried out according to the histological picture of the lesion. It is less often used as it increases anaesthetic and operation time. It also increases number of complications and morbidity. It has almost been replaced by FNAC which can provide equally good results much less invasi-vely.

IN VIVO OPTICAL SPECTROSCOPY (INVOS)

It is a new technique for evaluating risk of breast cancer. It is non ionizing and non imaging.

It evaluates the biochemical composition of the breast with spectro-photometer to provide a risk number related to carcinoma breast.

It has a sensitivity of 95% but very low specificity (4% only) and a positive predictive value of 21% for the detection of cancer[7].

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Fig-5.1 Skin preparation for fine needle aspiration

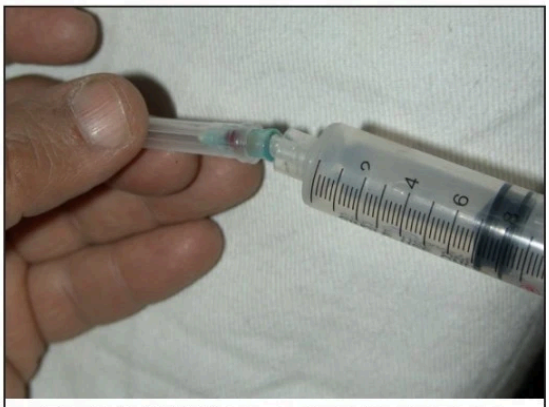

Fig-5.4 FNAC procedure in progress

Fig-5.2 Fine Needle Aspiration of a cyst in the breast

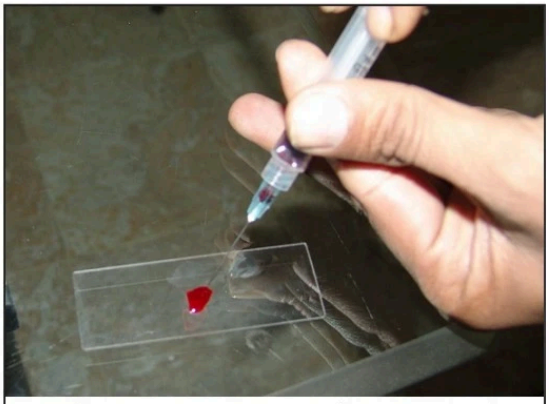

Fig-5.5 FNAC procedure in progress (preparation of specimen)

Fig-5.3 FNAC procedure in progress (Collection of specimen)

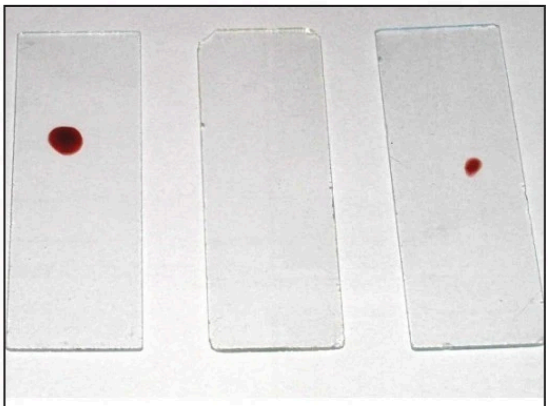

Fig-5.6 FNAC procedure in progress

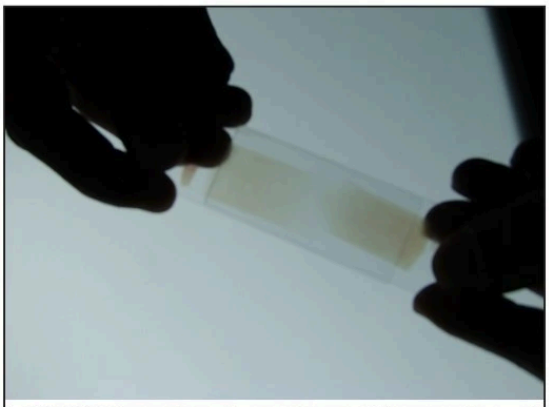

Fig-5.7 FNAC procedure in progress (Preparation of slides)

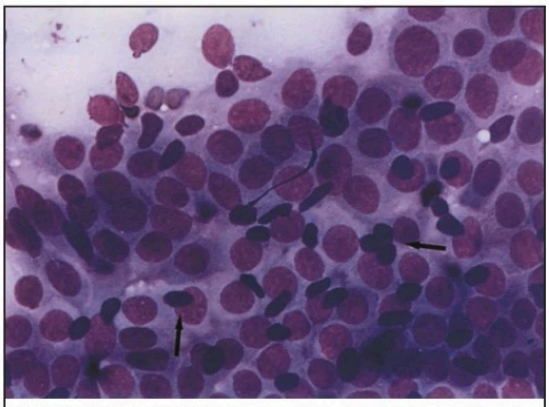

Fig-5.10 FNAC Common benign pattern

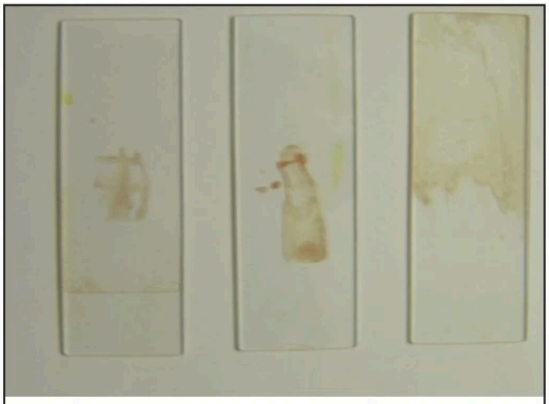

Fig-5.8 FNAC procedure in progress (Prepared specimens)

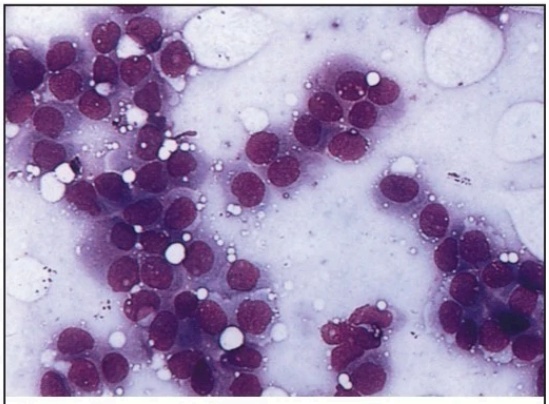

Fig-5.11 FNAC Common malignant pattern

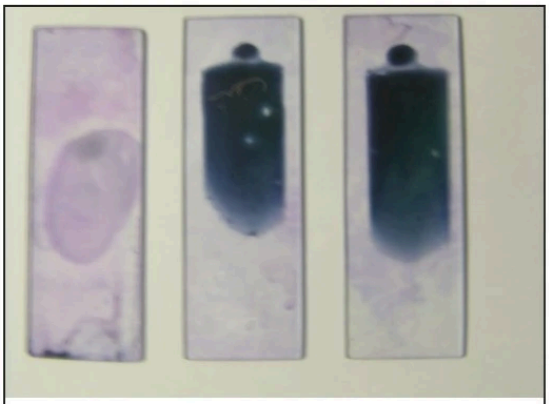

Fig-5.9 FNAC procedure in progress (Stained specimen)

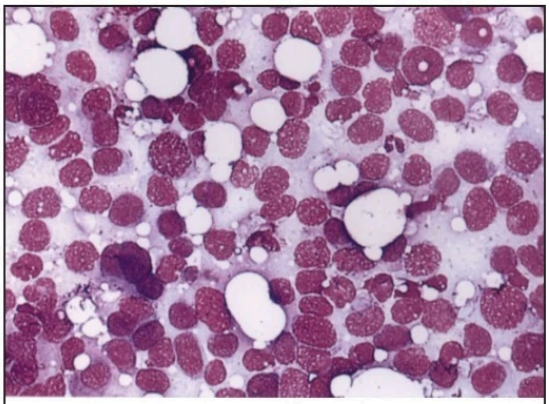

Fig-5.12 FNAC poorly differentiated carcinoma

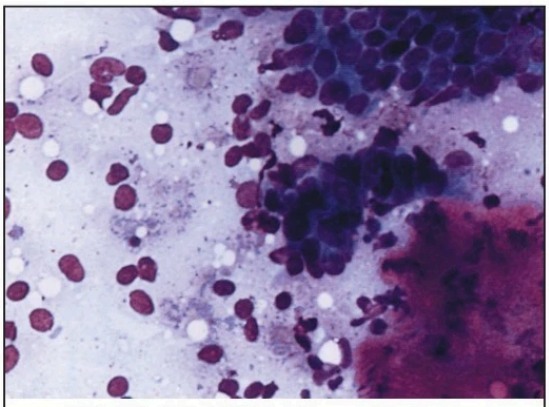

Fig-5.13 FNAC Fibroadenoma

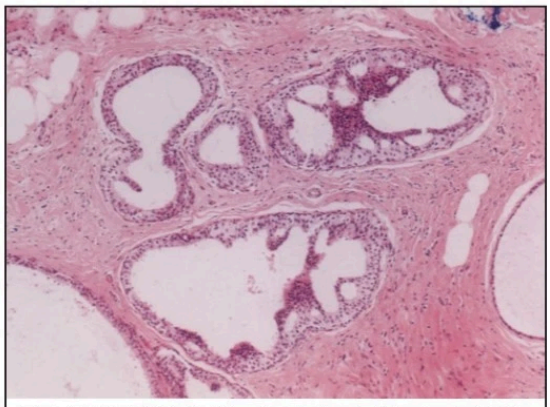

Fig-5.16 FNAC Atypical ductal hyperplasia

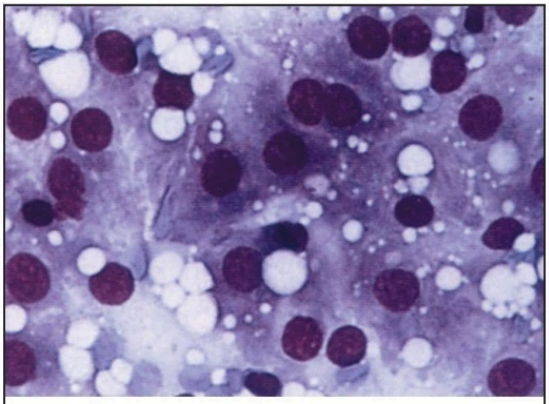

Fig-5.14 FNAC Lactating breast

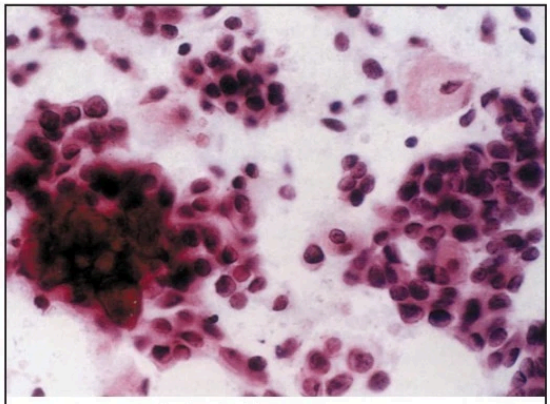

Fig-5.17 FNAC (DCIS) Ductal carcinoma in situ

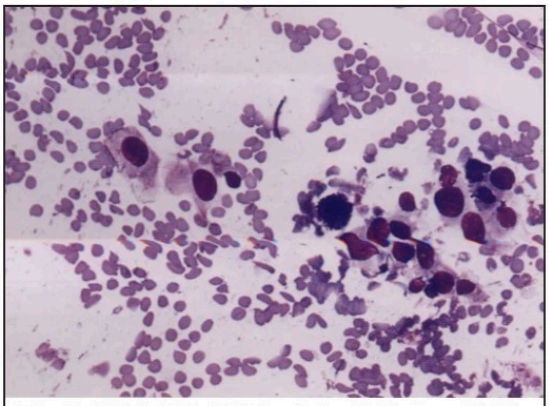

Fig-5.15 FNAC Atypical ductal hyperplasia

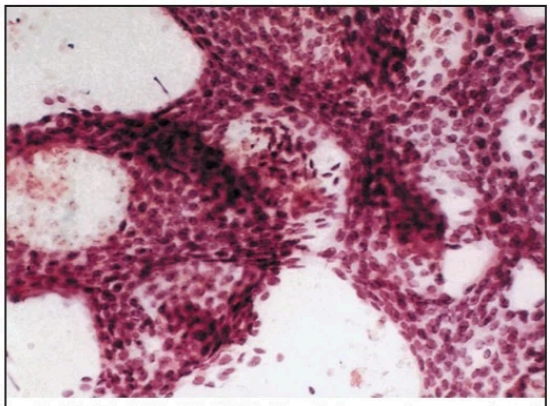

Fig-5.18 FNAC (DCIS) Ductal carcinoma in situ.

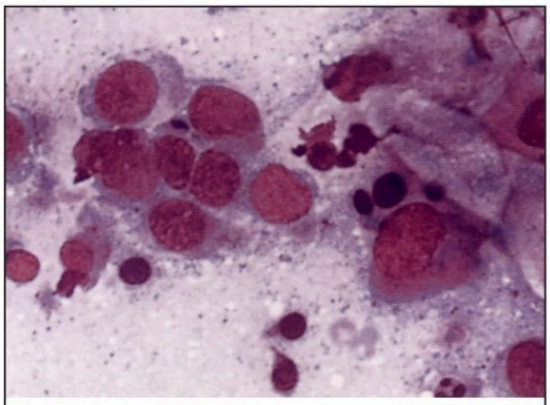

Fig-5.19 FNAC Paget's disease of nipple

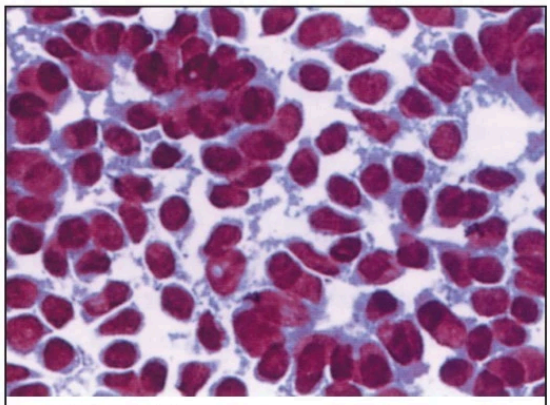

Fig-5.22 FNAC Invasive cribriform carcinoma

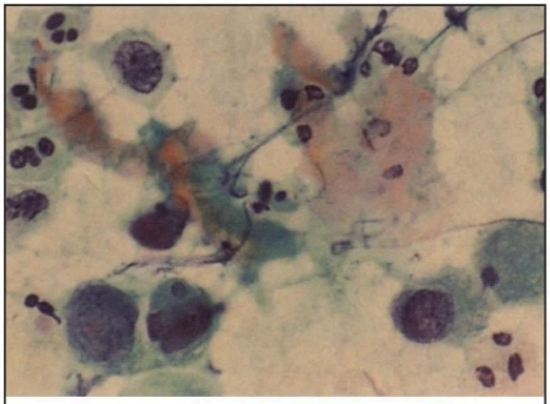

Fig-5.20 FNAC Paget's disease of nipple

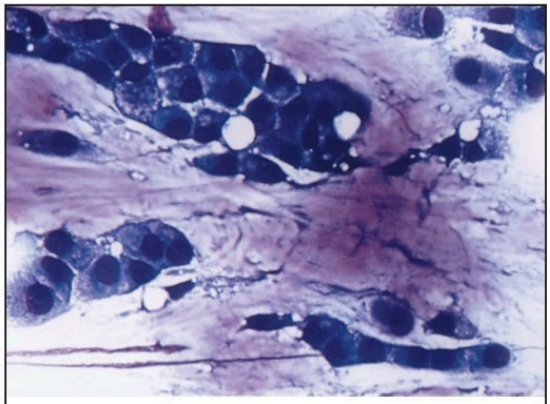

Fig-5.23 FNAC Colloid carcinoma

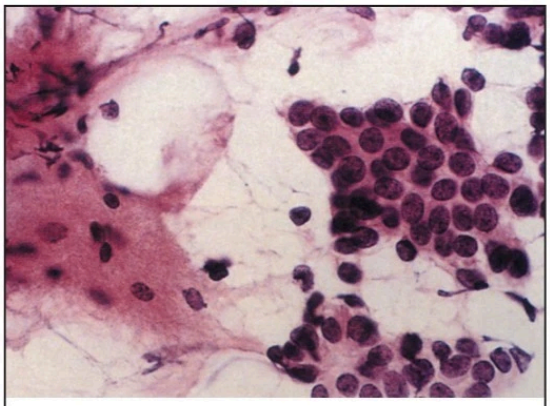

Fig-5.21 FNAC Tubular carcinoma

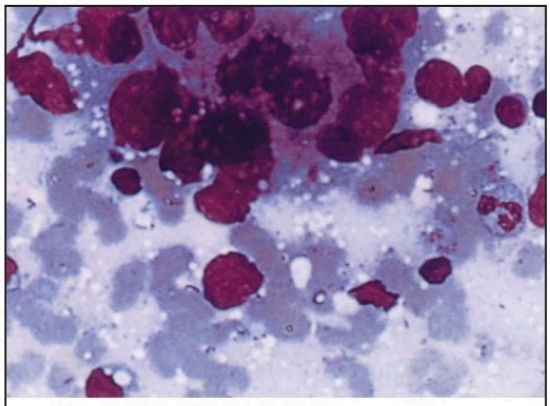

Fig-5.24 FNAC Medullary carcinoma

TRIPLE ASSESSMENT - 3 (CYTO HISTOLOGICAL EXAMINATION) 12

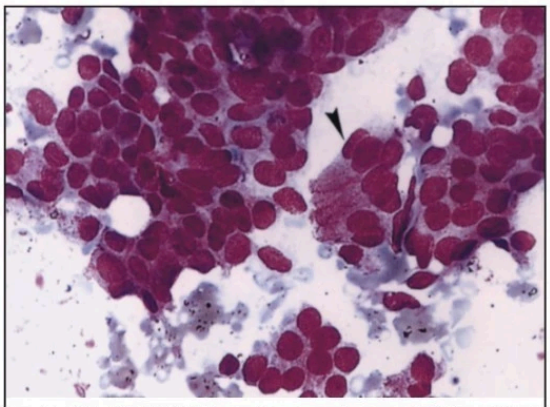

Fig-5.25 FNAC Carcinoma breast (Papillary)

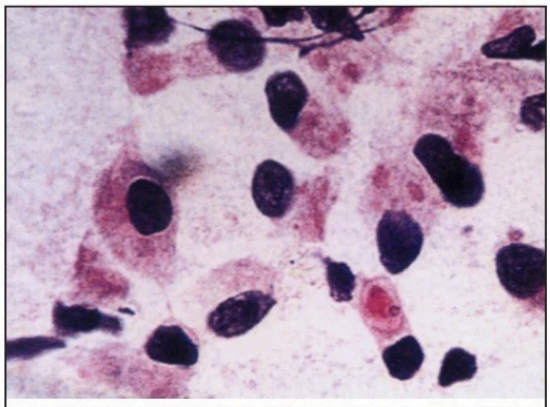

Fig-5.28 FNAC Infiltrating lobular carcinoma

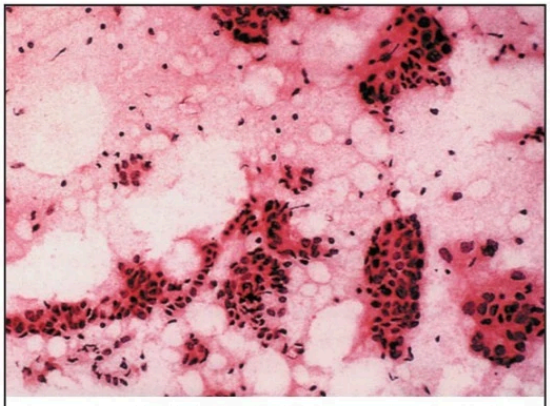

Fig-5.26 FNAC Carcinoma breast (tubular)

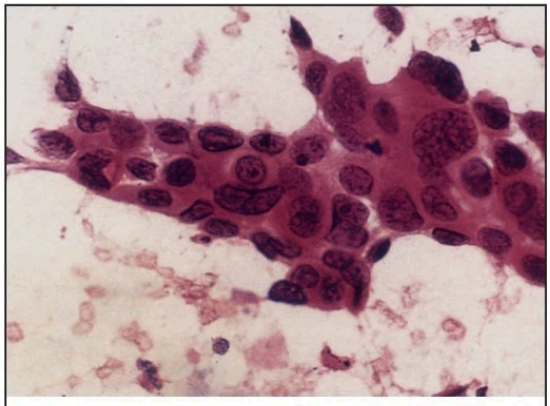

Fig-5.29 FNAC Comedo carcinoma with invasion

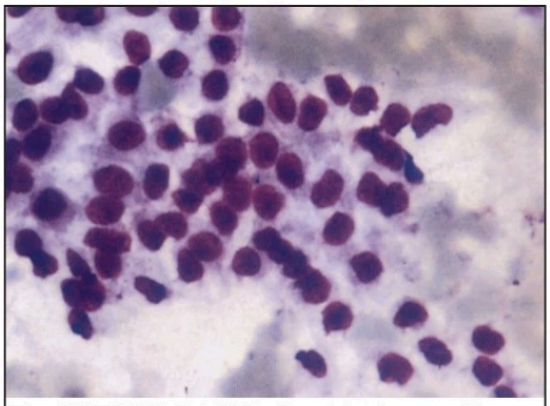

Fig-5.27 FNAC Infiltrating lobular carcinoma

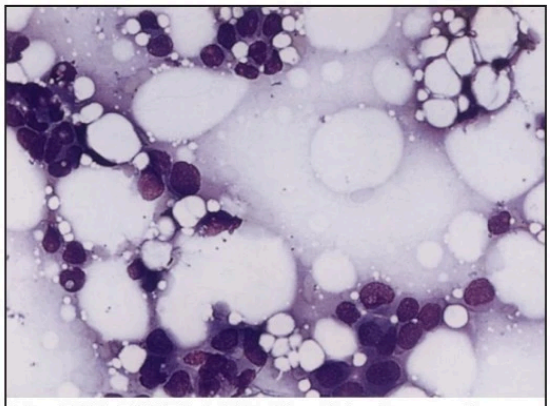

Fig-5.30 FNAC Infiltrating lobular carcinoma

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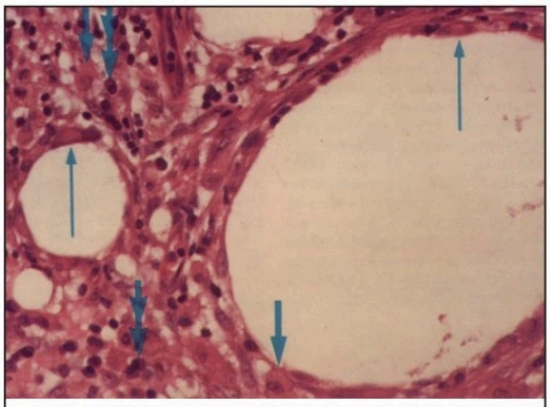


Fig-5.31 Fat necrosis breast (Histopath)

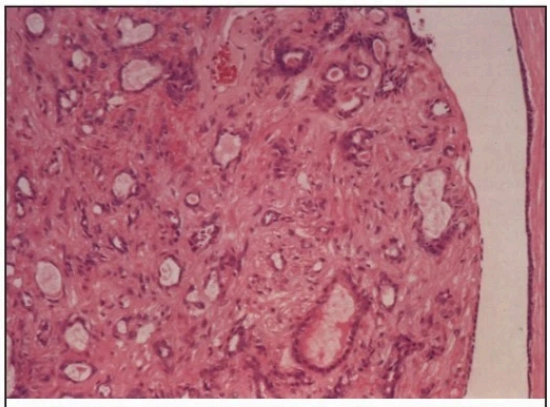


Fig-5.34 Intraductal papilloma breast (Histopath)

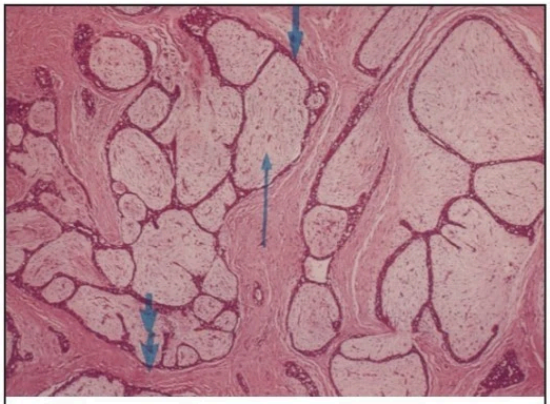


Fig-5.32 Fibroadenoma breast (Histopath)

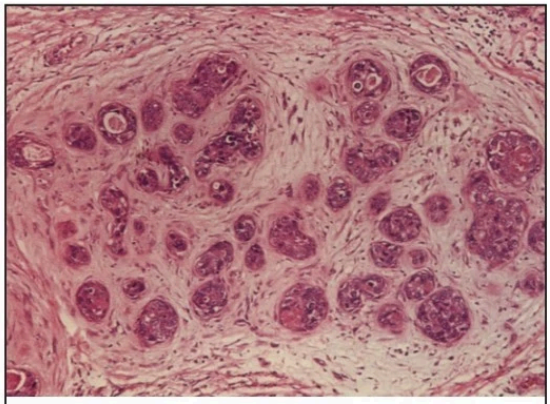


Fig-5.35 Intraductal carcinoma breast (Histopath)

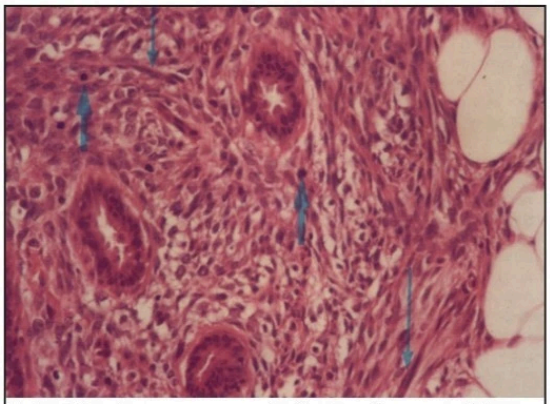


Fig-5.33 Cystosarcoma phyllodes breast (Histopath)

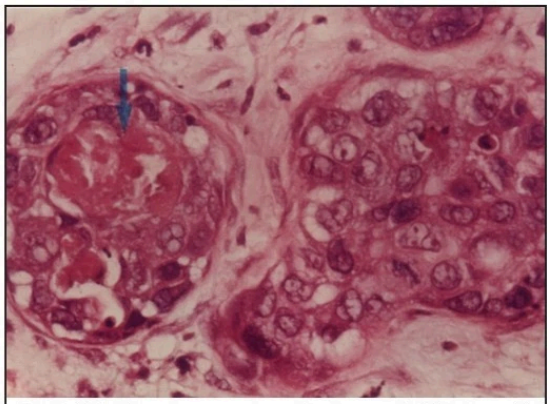


Fig-5.36 Carcinoma in situ breast (Histopath)

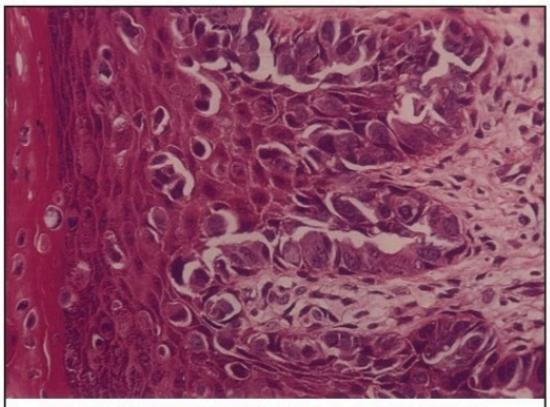


Fig-5.37 Paget's disease of breast

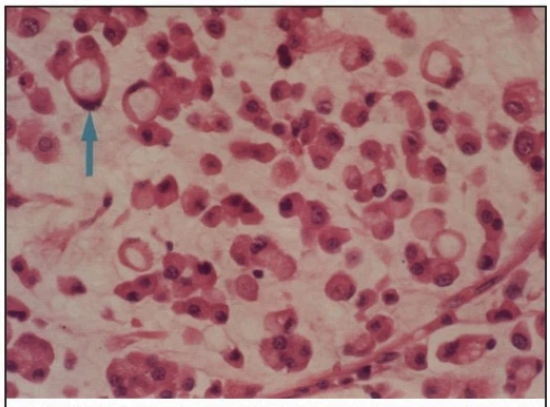


Fig-5.40 Infiltrating lobular carcinoma of breast

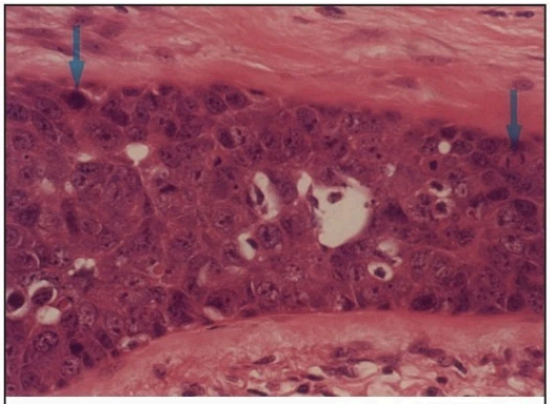


Fig-5.38 Paget's disease of breast

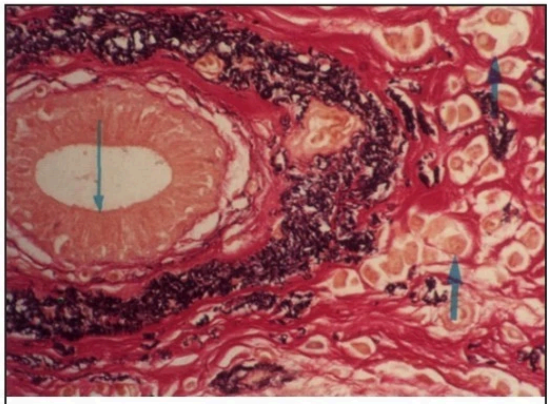


Fig-5.41 Invasive carcinoma breast

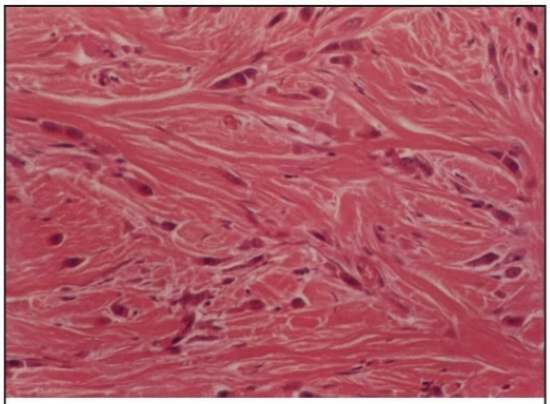


Fig-5.39 Invasive lobular carcinoma of breast

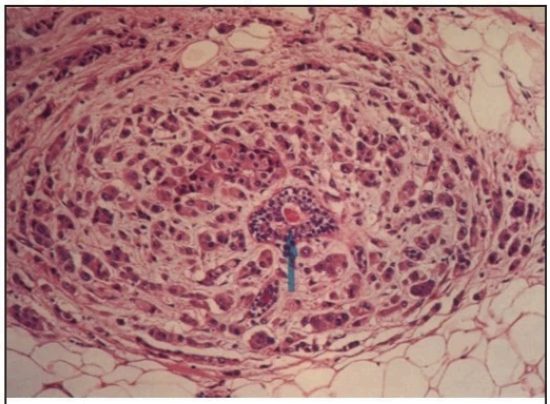
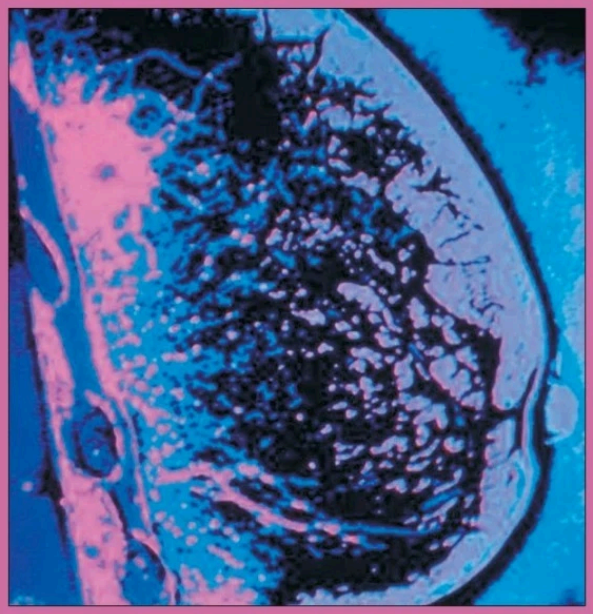


Fig-5.42 Lobular carcinoma of breast

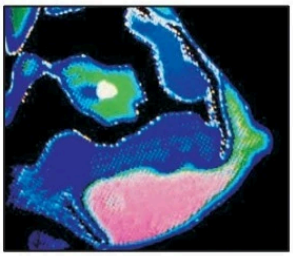
Chapter-06

Screening for Breast Problems



Objectives

- To detect the malignancy at earliest stage in a predefined female population.
- To collect baseline information for future comparison of breast lesions.
- To evaluate and monitor the high risk females for malignancy of breast.
- To assist in evaluation and management of symptomatic



SCREENING FOR BREAST PROBLEMS

Shuja Tahir, FRCS, FCPS

Screening for cancer breast, is investigating a given population for possibility of cancer breast.

Screening for carcinoma breast involves;

- Self examination of breast
- Clinical examination of breast
- Mammography (ultrasound, radiological and MRI).
- Cyto histological examination

Self examination and clinical examination have been found minimally helpful in early detection of carcinoma of breast which is the primary objective of screening for cancer breast.

Mammography has shown the ability to detect breast cancer with high sensitivity and specificity[1].

It is the only means to detect non-palpable cancers. It is the only effective investigation which helps in the early detection of breast lesions.

Cyto-histological examination is performed on palpable or suspicious but mammographically marked lesions which are not palpable.

SCREENING MAMMOGRAPHY

It is mammography of predefined female population of predetermined age in a selected locality.

Mammography both sonographic and radiological is commonly used for screening purpose. These are the investigations which can detect neoplastic lesions at the earliest.

M R I mammography is very helpful but it is used in high risk patients as it is expensive and less commonly available.

The general preconditions for successful screening programme are;

1. Disease should be curable.
2. Early detection should increase the chances of cure.
3. Screening procedure (diagnostic test) should be acceptable to target population.
4. The disease should be sufficiently common to warrant screening.

(WORLD HEALTH ORGANIZATION) PRINCIPLES OF SCREENING

- The condition should pose an important health problem.
- The natural history of disease should be well understood.
- There should be a recognizable early stage.
- Treatment at an early stage should be of more benefit than treatment started at a later stage.
- There should be a suitable test, which is acceptable to the population.
- There should be adequate facilities available for the diagnosis and treatment of abnormalities detected.
- Screening should be determined by the natural history of the disease for disease of insidious onset.
- The chance of harm to those screened should be less than the chance of benefit.
- The cost of a screening programme should be balanced against the benefit[3].

GUIDELINES FOR SCREENING

The underlying premise for breast cancer screening is that it allows for the detection of breast cancers before they become palpable.

Breast cancer is a progressive disease, and small tumors are more likely to be early stage disease, have a better prognosis, and are more successfully treated.

It leads to harms in women who undergo biopsy for abnormalities that are not breast cancer, as well as those who are over treated for ductal carcinoma in situ (DCIS) that might have been non progressive.
The benefits of screening should be assessed against the “limitations of screening and harms associated with screening”.

Mammography should begin at age 40 years for women at average risk. Women in their 20s and 30s should have clinical breast examination as part of routine physical examination at least every three years. At 40 years of age and thereafter, clinical breast examination should be done annually.

In elderly women, screening should be individualized based on potential benefits and risks of mammography in light of current health and life expectancy. “As long as a woman is in reasonably good health and would be candidate for treatment, she should continue to be screened with mammography.”

RISK FACTORS

Following factors help to plan the screening programme.

Age:
The risk of breast cancer increases

A significant number of patients develop cancer before 50 years of age and even before 35 years of age[3].

About 50% of all breast cancer patients are diagnosed in women aged 65 years or older. These patients respond well with surgery, radiotherapy and standard chemotherapy.

Older patients should also be included in screening programmes with mammography to detect the carcinoma at earlier stage[7].

Family medical history:
Having a first degree relative (or both) who had breast cancer, increases a woman's risk of developing breast cancer. If a woman's family member developed breast cancer before menopause, her risk is about 3 to 4 times greater than another woman of the same age who does not have a family history of breast cancer. If the family member developed breast cancer after menopause, the risk is about twice as great.

It is recommended that screening for familial breast cancer should start at the age of 30 years as it accounts for 10% of all breast cancer.

Genetic alterations:
Changes in certain genes(BRCA1, BRCA2 and others) make women more susceptible to breast cancer. In families in which many women have had the disease, BRCA gene testing can show whether a woman has specific genetic changes known to increase her susceptibility to breast cancer. Doctors may suggest ways to reduce the risk of breast cancer or to improve the detection of breast cancer in women who have the genetic alterations. Early mammography may be recommended for women who carry BRCA1or BRCA2 gene mutations.

Late childbearing:
Women who had their first child after the age of 30 have a greater chance of developing breast cancer than women who had their children at a younger age.

Radiation exposure:
Women whose breasts were exposed to significant amounts of radiation at a young age(especially those who were treated with radiation for childhood Hodgkin's disease or thyroid disease) have an increased risk for developing breast cancer. However , the amount of radiation received from a diagnostic chest x-ray during childhood is not significant and does not increase the risk for developing breast cancer.

Previous breast biopsies:
Two breast biopsies done for a noncancerous (benign) breast disease, especially for atypical hyperplasia show an increased risk of developing breast cancer.

Hormone replacement therapy:
The use of daily estrogen 0.625 mg plus progestin 2.5 mg for longer than 4 years

definitely warrants diagnosis at the earliest. The disease should be detected much before it is palpable.

CONTROVERSIES IN SCREENING

The new guidelines address some controversial issues of breast cancer screening;

What is the efficacy (and potential risk) of breast self-examination?

What is the efficacy (and potential risk) of clinical breast examination?

At what age should mammographic screening begin for women of average risk and above average risk?

At what age should mammographic screening be discontinued in elderly women or women with co-morbid conditions?

What is the role of new technologies in screening practices?

The major conclusions are;

For women at average risk:
Begin mammography at age 40 years.

Women should have annual or bi-annually mammography between 40-70 years of age depending upon physical examination and risk factors.

Women should have yearly mammography after 50 years of age. The frequency can be reduced to three yearly if two consecutive mammograms are normal.

For women in their 20s and 30s, do clinical breast examination at least every three years.

Asymptomatic women aged 40 years and older should continue to receive a clinical breast examination as part of a periodic health examination, preferably annually.

The benefits, limitations, and implications of breast self-examination (BSE) should be explained to women in their 20s and older. Those opting to perform regular BSE should have their technique reviewed during their periodic health examination.

Beginning in their 20s, women should be told about the benefits and limitations of breast self-examination (BSE), including the importance of prompt reporting of any new breast symptoms.

Women who choose to do BSE should receive instruction and have their technique reviewed on the occasion of a periodic health examination.

Women may choose not to do BSE or to do BSE irregularly. Women should be informed about the benefits, limitations and potential harms associated with regular screening.

other than mammography and physical examination, such as ultrasound or magnetic resonance imaging, could be considered. But the evidence currently available is insufficient to justify recommendations for any of these screening approaches.

Pre-menopausal women with strong family history should start mammography as early as 35 years of age or 5 years younger than youngest affected family member[3].

Screening for familial breast cancer should start at 30 years of age[3].

Screening of 100% population may not always be easily feasible. Breast screening program in UK aims to screen 70% of target population with built in quality assurance.

One of the goals of National Cancer Institute (NCI) to reach more than 80% of eligible women in mammography screening by year 2000 yet remains as a challenge. The failure to achieve this goal is due to[3];

- Complex and lengthy examination process.
- It is not available to majority of women living in remote areas[4].

It has been suggested that average doubling time for breast cancer growth is about 100 days and it takes nearly 6-7 years or longer before it becomes potentially detectable by physical examination or mammography.

The screening mammography is performed in all women between 40-70 years of age to achieve optimal results[2,10].
Patients with mutations in one of the breast cancer susceptibility gene face about 90% life time risk to develop breast cancer.

95% screen detected cancers are smaller in size, better differentiated and node negative when compared with symptomatic cancers[5].

We can anticipate 40% reduction in mortality from breast cancer by screening women above 50 years of age and only 5% reduction by screening younger women[4].

Mammograms must be done regularly (every 12 to 18 months) to get the full benefits of screening and to reduce the risk of dying from breast cancer. Regular mammograms prevent fewer breast cancer deaths in younger women than they do in elderly women, because breast cancer is more common in elderly women.

There is 60-80% increase in the number of women in western world having mammographic screening. It has resulted in early detection of early stage carcinoma breast and reduction in the mortality rate[5].

assessment is essential to provide risk benefit analysis prior to initiating interventions designed to lower breast cancer risk[8].

The women should be informed about the potential benefits and risks of screening mammography. They should be helped to make a decision about their age to join in screening programme.

The value of screening mammography is still debatable whether the cost justifies the benefits. The question is whether any better method of screening is available? This is the situation after nine (9) randomized trials and nineteen (19) meta-analyses to determine the cost benefit justification[9,19].

The breast cancer screening is better with mammography than without.

70% of cancers were detected with annual screening as compared to 57% without screening.

Criticism also includes;

- Selection Bias: (some women volunteered for screening due to fear about breast lump or other changes).
- Lead time Bias: (Cancers always get detected with or without screening but earlier with screening).
- Length Bias: (certain cancers will be detected later any way because of slower growth).
- Interval cancers: (fast growing tumors that surface in between screening periods).

Screening resulted in 25% fewer deaths and survival curves began to separate at 1-2 years after initiation of screening[9,10].

Some critics don't get persuaded by the real value of mammographic screening of women in their 40s. Several factors have contributed to this reluctance, including ;

- A lower cancer incidence in this group.
- Fewer number of women in this age group being screened.
- Dense breasts in younger women
- Faster tumor growth rates.
- Shorter lead time.
- Higher survival rates in younger women in spite of underlying diagnosis.

Longer follow-up with younger women may clearly reveal benefits of screening measures.

An average 18% mortality reduction was observed with follow up ranging

Year	Breast Cancer Decline
1987	28.8%
1992	55.2%
1998	66.9%

This is the reason for supporting mammographic screening of women of 40 years of age[11,12,13].

The breast cancer mortality rate has decreased by 1% each year over past

The incidence of breast cancer detection increased by 36% from 1980-1999, the rate of mortality dropped by 17%[14,15,16].

The bulk of mammographically detected breast cancer has been ductal carcinoma in situ (DCIS). The absolute increase in breast cancer detection (9%) exceeds the decline in breast cancer mortality and it implies that something other than mammography is at work. It may be treatment of DCIS by mastectomy rather than breast conservation[14,15,16].

Almost 75% of lesions identified on mammography ultimately prove to be benign (false positive results)[17,18].

CONCLUSIONS

Following conclusions can be drawn from various studies.

Routine mammography can decrease breast cancer mortality.

Mammography has significant and important limitations.

Many new technologies have the potential to improve breast cancer screening and diagnosis but must be tested in clinical trials.

A greater understanding of breast tumor biology is needed.

The ultimate objective is better methods of correct early detection of lesions leading to cancer breast[19].

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Chapter-07

Breast Feeding

Objectives

- To understand the importance of breast feeding for both mother & child.
- To understand the normal physiological changes in breast during pregnancy, lactation and after lactation.
- To understand the preparation and care of the breast before & during lactation.

BREAST FEEDING

Mahnaaz Roohi, FRCOG

God Almighty is the creator of the whole world and is responsible for the bread and butter of all human beings (man, animals and plants). The human beings are considered as modernized and civilized mammals.

God has made provision of two breasts to each woman so that they can breast feed their young ones. There is no need to train the women as breast feeding is a natural phenomena and all the mammals feed their young ones without any training. When a lady breast feeds a baby, he/she will be better equipped in intelligence and psychological behavior and will be immune to certain contagious diseases.

New parents want to give their baby the very best. As far as nutrition is concerned, the best first food for babies is breast milk[1].

The mothers milk is described as an un-equaled food for the baby except in special circumstances (hare lip, cleft palate, extreme prematurity). The formula milks in no way can give the same advantage to a new born. The bonding between the infant and mother does not successfully develop without breast feeding. All women have an ability to breast feed but there are certain reservations as she requires five hundred calories more than the normal diet.

Breast feeding should start soon after the baby is born even before the umbilical cord is cut, the baby is put to the breast. This promotes successful breast feeding and also helps in lowering the duration of third stage of labor. It is very important that the initial milk which is thick and full of calories “colostrum”. should be definitely fed to the baby because it provides enough calories to the baby for survival and also contains the antibodies and immune factors which prevent diseases in the new born at least for 3 months.

More than two decades of research have established that breast milk is perfectly suited to nourish infants and protect them from illness. Breast-fed infants have lower rates of hospital admissions, ear infections, diarrhoea, rashes, allergies, and other medical problems than bottle-fed babies.

illnesses, including pneumonia, botulism, bronchitis, staphylococcal infections, influenza, ear infections, and German measles. Furthermore, mothers produce antibodies to whatever disease is present in their environment, making their milk custom-designed to fight the diseases their babies are exposed to as well.

A breast-fed baby's digestive tract contains large amounts of Lactobacillus bifidus, beneficial bacteria that prevent the growth of harmful organisms. Human milk straight from the breast is always sterile, never contaminated by polluted water or dirty bottles, which can also lead to diarrhoea in the infant.

Human milk contains at least 100 ingredients not found in formula milk. No babies are allergic to their mother's milk, although they may have a reaction to something the mother eats. If she eliminates it from her diet, the problem resolves itself.

Sucking at the breast promotes good jaw development as well. It's harder work to get milk out of a breast than a bottle, and the exercise strengthens the jaws and encourages the growth of straight, healthy teeth. The baby at the breast also can control the flow of milk by sucking and stopping. With a bottle, the baby must constantly suck or react to the pressure of the nipple placed in the mouth.

Nursing may have psychological benefits for the infant as well, creating an early attachment between mother and child. At birth, infants see only 12 to 15 inches, the distance between a nursing baby and its mother's face. Studies have found that infants as young as 1 week prefer the smell of their own mother's milk. When nursing pads soaked with breast milk are placed in their cribs, they turn their faces toward the one that smells familiar.

Many psychologists believe the nursing baby enjoys a sense of security from the warmth and presence of the mother, especially when there's skin-to-skin contact during feeding. Parents of bottle-fed babies may be tempted to prop bottles in the baby's mouth, with no human contact during feeding. But a nursing mother must cuddle her infant closely many times during the day. Nursing becomes more than a way to feed a baby; it's a source of warmth and comfort.

Counseling of a patient for breast feeding should start during the antenatal period and the patient should be taught how to breast feed and examine their own breasts. If they find a lump or something else obviously they will consult a surgeon. Other wise the size of breast is not important for the quantity of milk produced. The common problem which women complain of is invertion of nipples. But one should remember that when breast feeding starts and the baby sucks this is called

Breast feeding should be on the demand of the child rather than watching the time on a watch.

BENEFITS TO MOTHERS

Breast-feeding is good for new mothers as well as for their babies. There are no bottles to sterilize and no formula to buy, measure and mix. It may be easier for a nursing mother to lose the pounds of pregnancy as well, since nursing uses up extra calories. Lactation also stimulates the uterus to contract back to its original size.

A nursing mother is forced to get needed rest. She must sit down, put her feet up, and relax every few hours to nurse. Nursing at night is easy as well. No one has to stumble to the refrigerator for a bottle and warm it while the baby cries. If she's lying down, a mother can doze while she nurses.

Nursing is also nature's contraceptive--although not a very reliable one. Frequent nursing suppresses ovulation, making it less likely for a nursing mother to menstruate, ovulate, or get pregnant. There are no guarantees, however.

Mothers who don't want more children right away should use contraception even while nursing. Hormone injections and implants are safe during nursing, as are all barrier methods of birth control. The labeling on birth control pills says if possible another form of contraception should be used until the baby is weaned. Breast-feeding is economical also. Even though a nursing mother works up a big appetite and consumes extra calories, the extra food for her is less expensive than buying formula for the baby. Nursing saves money while providing the best nourishment possible.

POSSIBLE PROBLEMS

For all its health benefits, breast-feeding does have some disadvantages. In the early weeks, it can be painful. A woman's nipples may become sore or cracked. She may experience engorgement more than a bottle-feeding mother, when the breasts become so full of milk they're hard and painful. Some nursing women also develop clogged milk ducts, which can lead to mastitis, a painful infection of the breast. While most nursing problems can be solved with home remedies, mastitis requires prompt medical care.

Another possible disadvantage of nursing is that it affects a woman's entire lifestyle. A nursing mother with baby-in-tow must wear clothes that enable her to nurse anywhere, or she'll have to find a private place to undress. She should eat a balanced diet and she might need to avoid foods that irritate the baby. She also shouldn't smoke, which can cause vomiting, diarrhea and restlessness in the baby, as well as decreased milk production.

mothers can get away between feedings if they need a break.

Finally, some women just don't feel comfortable with the idea of nursing. They don't want to handle their breasts, or they want to think of them as sexual, not functional. They may be concerned about modesty and the possibility of having to nurse in public. They may want a break from child care to let someone else feed the baby, especially in the wee hours of the morning.

If a woman is unsure whether she wants to nurse, she can try it for a few weeks and switch if she doesn't like it. It's very difficult to switch to breast-feeding after bottle-feeding is begun.

If she plans to breast-feed, a new mother should learn as much as possible about it before the baby is born. Obstetricians, pediatricians, childbirth instructors, nurses, and midwives can all offer information about nursing. But perhaps the best ongoing support for a nursing mother is someone who has successfully nursed a baby.

There are certain constraint to breast feeding.

- Either the patient is not motivated herself or cultural and family constraints reduce the mobility and behaviour of the patient.
- Inadequate knowledge of the steps to take where breast feeding fails.
- Pre-lacteal feeding is a custom in our country so it carries on.

HARMFUL EFFECTS OF PRE-LACTEAL FEEDS

- Diarrhea & infections.
- Ghurti can act as purgative which can lead to early expression of milk.
- Cow’s milk is the closest to human milk but it still has many disadvantages.
- Pre-lacteal feed make the new born nipple conscious as by nature humans are lazy and that is easier for them.

PROPERTIES OF BREAST MILK

It provides enough for that age. It contains mild laxative, so constipation is not a problem in these children.
It prevents jaundice.
It contains all the nutrients that the new born needs.
There is no reason of giving any supplement even in the form of water.

TIPS FOR BREAST-FEEDING SUCCESS

It's helpful for a woman who wants to breast-feed to learn as much about it as possible before delivery, while she is not exhausted from caring for an infant around-the-clock. The following tips can help foster successful nursing:

EARLY START
Nursing should begin within an hour after delivery if possible, when an infant

NURSE ON DEMAND

Newborns need to nurse frequently, at least every two hours, and not on any strict schedule. This will stimulate the mother's breasts to produce plenty of milk. Later, the baby can settle into a more predictable routine. But because breast milk is more easily digested than formula, breast-fed babies often eat more frequently than bottle-fed babies.

NO SUPPLEMENTS

Nursing babies don't need sugar, water or formula supplements. These may interfere with their appetite for nursing, which can lead to a diminished milk supply. The more the baby nurses, the more milk the mother will produce.

DELAY ARTIFICIAL NIPPLES

It's best to wait a week or two before introducing a pacifier, so that the baby doesn't get confused. Artificial nipples require a different sucking action than real ones. Sucking at a bottle could also confuse some babies in the early days. They, too, are learning how to breast-feed.

AIR DRY

In the early postpartum period or until her nipples toughen, the mother should air dry them after each nursing to prevent them from cracking, which can lead to infection. If her nipples do crack, the mother can coat them with breast milk or other natural moisturizers to help them heal. Vitamin E oil and lanolin are commonly used, although some babies may have allergic reactions to them. Proper positioning at the breast can help prevent sore nipples. If the mother's very sore, the baby may not have the nipple far enough back in his or her mouth.

WATCH FOR INFECTION

Symptoms of breast infection include fever and painful lumps and redness in the breast. These require immediate medical attention.

EXPECT ENGORGEMENT

A new mother usually produces lots of milk, making her breasts big, hard and painful for a few days. To relieve this engorgement, she should feed the baby frequently and on demand until her body adjusts and produces only what the baby needs. In the meantime, the mother can take over-the-counter pain relievers, apply warm, wet compresses to her breasts, and take warm baths to relieve the pain.

EAT RIGHT, GET REST

To produce plenty of good milk, the nursing mother needs a balanced diet that includes 500 extra calories a day and six to eight glasses of fluid. She should also rest as much as possible to prevent breast infections, which are aggravated by fatigue.

EXCLUSIVE BREAST FEEDING

Exclusive breast feeding means that during that time period nothing else (like formula milks or even water) should be

most of the women who breast feed do not ovulate).

The baby should be fed from both breasts so that the milk is not wasted from any breast.

Sore nipple is one of the disadvantages of sucking but the patient can be given soothing creams and lotions which can solve the problem or if the cracks in the nipple are too many than they can use a nipple sheath.

After all, nothing is perfect and some potential problems can arise during breast feeding such as;

- Some people may repeat negative practices such as giving pre-lactel feeds and water.
- A Woman may not feel confident enough and think incapable to breast feed.
- Inadequate maternal feed.
- Sore nipples and mastitis

It is important that the patient should be explained in the antenatal period about optimum food intake during pregnancy and lactation.

Counsel the women and her spouse and family about improving her diet during pregnancy and lactation.

Assess the dietary intake of pregnant and lactating women.

There should be no supplementary formula milk and it should be condemned and its marketing should be unlawful.

Counsel the mothers about the quantity, quality, frequency and consistency of food for an infant upto 1year of age.

Preferably exclusive breast feeding is for 4-5 months but a women should breast feed along with weaning for two years.

GUIDELINES OF NORMAL NUTRITION IN INFANTS

- Give breast milk at least 6 times a day and none on demand.
- Feed semisolid foods three times a day with a spoon at each feeding after the age of 4-6 months.

Initially a women having a baby for the first time may run into problems and she needs counseling otherwise she will develop psychological problems which are collectively known as “purple blues”.

We keep on using the term confusion of nipple. Now what is meant by it. The baby has already sucked through a feeder nipple and may have confusion in breast feeding. The mother should keep the baby with her during the day and night. Isolated nurseries are not required in this modern era.

Correct positioning of the baby in age more than 4 months, expressed milk or

- If the infant unfortunately dies.
- No contagious disease, even hepatitis is not an absolute contra-indication for breast feeding.
- Professional mothers do not have the advantage and facilities to breast feed on demand (arrangement at work place should be made).
- When the women herself is poorly nourished.
- When a baby in born with congenital abnormalities like hare lip and cleft palate.
- Oral thrush; because it also contaminate the mother.
- One should not breast feed the baby for 48 hours but obtain the milk of the mother every 3 or 4 hour so that lactating reflex which is initiated by prolactin is not terminated in early onset jaundice which does not clear and there is poor excretion of bilirubin. The breast feeding can be resumed later on.
- Early onset fetal (non physiological) jaundice is an absolute contra-indication to breast feed for a limited period.
- If the nipple areola complex has sores or infection then obviously breast feeding should be carried out after treating the sores.

The advantages to the mother and babies are innumerable.

- Mother can breast feed in which ever position they like.
- The breast milk is always supplied at body temperature. So heating and cooling is not a problem.
- Breast milk is the ideal and enough food for the baby. This causes less stress to the mother and also the family. Because the mother doesn't remain irritable.
- It should be remembered, 80% of our population lives in rural areas. Where the usual feed which is given to the baby is breast milk. As formula milks are too expensive for them (this is blessing in disguise).

If the animals can breast feed their young ones without any counseling or training. The human beings are much more intelligent and breast feeding is a natural phenomena which should not be converted to stop feeding.

Breast feeding is associated with reduction in the incidence of breast cancer in the mother.

It is a natural way of family planning as ovulation usually does not occur during breast feeding. It should be recommended to stop the marketing and promotion of formula milks. Breast feeding should be the sole type of feeding the new born.

MEDICINES AND NURSING MOTHERS

Most medications have not been tested in nursing women, so no one knows exactly how a given drug will affect a breast-fed child. Since very few problems have been reported,

- Acetaminophen
- Many antibiotics
- Antiepileptics (although one, Primidone, should be given with caution)
- Most antihistamines
- Alcohol in moderation (large amounts of alcohol can cause drowsiness, weakness, and abnormal weight gain in an infant)
- Most antihypertensives
- Aspirin (should be used with caution)
- Caffeine (moderate amounts in drinks or food)
- Codeine
- Decongestants
- Ibuprofen
- Insulin
- Quinine
- Thyroid medications

DRUGS THAT ARE NOT SAFE WHILE NURSING

Some drugs can be taken by a nursing mother if she stops breast-feeding for a few days or weeks. She can pump her milk and discard it during this time to keep up her supply, while the baby drinks previously frozen milk or formula.

Radioactive drugs used for some diagnostic tests like Gallium-69, Iodine-125, Iodine-131, or Technetium-99m can be taken if the woman stops nursing temporarily.

Drugs that should never be taken while breast-feeding include:

Bromocriptine (Parlodel):
A drug for Parkinson's disease, it also decreases a woman's milk supply.

Most Chemotherapy Drugs for Cancer:
Since they kill cells in the mother's body, they may harm the baby as well.

Ergotamine (for migraine headaches):
Causes vomiting, diarrhea, convulsions in infants.

Lithium (for manic-depressive illness):
Excreted in human milk.

Methotrexate (for arthritis):
Can suppress the baby's immune system.

Drugs of Abuse:
Some drugs, such as cocaine and PCP, can intoxicate the baby. Others, such as amphetamines, heroin and marijuana, can cause a variety of symptoms, including irritability, poor sleeping patterns, tremors, and vomiting. Babies become addicted to these drugs.

Tobacco Smoke:
Nursing mothers should avoid smoking. Nicotine can cause vomiting, diarrhea and restlessness for the baby, as well as decreased milk production for the mother. Maternal smoking or passive smoke may increase the risk of sudden infant death syndrome (SIDS) and may increase respiratory and ear infections.

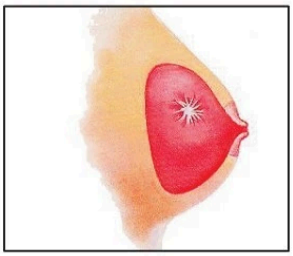
REFERENCES

Chapter-08

Presentation of Breast Diseases - 1
Breast Lumps

Objectives

- To find out the presence of lump with its exact site.
- To find out the nature of lump whether inflammatory, benign, malignant or developmental aberration.
- To stage the lump in cases of malignancy.
- To investigate methodically and appropriately.
- To plan management correctly.
- To follow up the patients adequately.



PRESENTATION OF BREAST DISEASES -1

BREAST LUMPS

Shuja Tahir, FRCS, FCPS

The breast diseases present in different ways. Sometimes the problem of adjacent structures may present as breast problem. A very careful triple assessment helps to reach accurate diagnosis and management of such patients. These presentations can be of;

1. Breast diseases.
2. Associated diseases.

BREAST SWELLINGS

These could be swellings of the whole breast or may be discrete or isolated lumps.

Breast swellings could be bilateral or unilateral.

BILATERAL BREAST SWELLINGS
PHYSIOLOGICAL

These could be seen in following conditions;

1. Pregnancy

The size of breast increases during pregnancy as the mammary glands prepare for lactation under the influence of various hormones.

The examination of breast is one of the important parts of diagnosis of pregnancy or even pervious pregnancies. The color changes of areola are also typical due to pregnancy.

2. Lactation

The breast starts its actual function of production of milk soon after delivery under the influence of various hormones. The size of breast reduces after the baby is fed and increases due to engorgement of lactiferous ducts due to production of milk few times during day and night. The size of breast reduces and the involution of mammary glands and duct occurs after weaning of the baby.

3. Macromastia / Hypertrophic breasts

Macromastia is the massive enlargement of breast unilateral or bilateral, disproportionate to the growth of remainder of the body.

Rapid and massive breast hypertrophy may occur occasionally at puberty or during pregnancy or rarely even other wise. The size of breast eventually becomes bothersome, or incapacitating to the patient[2].

Pregnancy related breast hypertrophy can be arrested or reversed by reducing serum prolactin level with bromocriptine therapy.

Extreme tenderness, erythema and edema of breast can be treated surgically which may not always be cosmetically acceptable[3].

DEVELOPMENTAL SWELLINGS

The common cause of such swelling is;

ANDI (Abnormalities of normal development and involution).

Inflammatory breast swellings.

Acute mastitis is a common condition of inflammatory nature.

Miscellaneous Bilateral Breast swellings

Gynaecomastia or Hypertrophy of breast in males is seen after stilboesteral therapy for carcinoma prostate. It is also seen in liver failure as the oestrogen levels are raised due to failure of detoxification in the liver. It is enlargement of a normal breast. The enlargement is uniform. It is more commonly seen in males than females. It is diagnosed clinically. Treatment decision and plan is simple. Reassurance or subcutaneous mastectomy can be performed.

Prosthesis of correct size and shape may be implanted according to female patient's choice for good cosmetic effects.

UNILATERAL BREAST SWELLINGS

1. Fibro adenosis of new born.
2. Puberty.
3. Unilateral hypertrophy.

DISCRETE OR ISOLATED LUMP IN BREAST

These could be malignant or innocent benign in nature.

BENIGN SWELLINGS

FIBROADENOMA

It is the most common benign tumor of the female breast. It consists of both fibrous tissue and glandular tissue. It is common before 30 years of age but no age is immune. It has a rubbery feel and moves around easily. It is solid, round and painless. it occurs twice as common in Afro-American females than American females. It can enlarge during pregnancy and breast feeding.

A fibroadenoma can be diagnosed clinically with fair degree of certainty.

It may be excised surgically if patient wishes to have it removed or doctor advises its excision. It is treated as a day case surgery.

The fibroadenomas don't recur unless excised incompletely. Another fibroadenoma may grow in any one of the breast in future.

The giant fibroadenoma grows rapidly and attains large size.

It is bigger than 4-5 cm in diameter. The breast is enlarged, nipple may be displaced, overlying skin is shiny, veins are dilated. It may be present in one breast.

It has higher incidence at two different age groups. It presents at 14-18 years of age and 45-50 years of age. Treatment is cosmetic enucleation.

CYST

Cyst results from the enlargement of the breast lobule or lactiferous duct, It is related to altered hormonal stimulation and endo-organ response. It enlarges and becomes tender before the menstrual period starts.

It can occur at any age after puberty but commonly presents in the perimenopausal years (35-50 years old female).

The cysts can regress spontaneously after menstrual periods or develop after oestrogen replacement therapy[1].

The cyst may demonstrate a thin rim of calcification on mammographic examination. The cyst may occasionally rupture during compression while performing mammography[2].

A cyst can also be clinically diagnosed with reasonable confidence. Usually no edges can be palpable. It is best confirmed by aspiration. The cyst disappears completely after aspiration. It can be easily diagnosed ultrasonographically.

The patient is followed up every month for the reappearance of the lump. The cyst fluid is cytologically examined and if there is any doubt or the lump does not disappear completely after aspiration or reappears within few days, excision biopsy of the lump is performed.

The patient is followed up for at least 2-3 months after aspiration of the cyst for spontaneous resolution. Excision biopsy is performed in young women with residual breast masses[3].

There is increasing evidence that multiple recurrent cysts are associated with small but significant increase in breast cancer risk[4].

A.N.D.I.
FIBROADENOSIS

breast tissue (ducts and glands) to enlarge and breast to retain fluid. The breast becomes normal after fall in the hormonal levels. Some areas of breast may respond excessively and may remain enlarged and nodular even after normalization of hormone levels.

This can be suspected on clinical examination. The lesions may be present in both the breasts. The feeling of the breast tissue is nodular. There is history of variable degree of tenderness during menstrual cycle. Further confirmation can be done by FNAC, trucut needle or excision biopsy.

GALACTOCELE

It is a rare subareolar cyst presenting in relation with lactation. It is less common problem than thought.

It is commonly seen in women who have recently stopped breast feeding. Occasionally it may occur during lactation as well. It consists of ducts distended with milk.

Aspiration confirms the diagnosis as it drains the milk and the lump disappears.

Secondary infection may lead to breast abscess formation.

FNAC, trucut or excision biopsy must be performed in doubtful cases.

PHYLLOIDES TUMOUR

It is a variety of fibroadenoma which usually presents in women of age around 35 years as a lobulated mass.

It is giant fibroadenoma and its cut sections show leaf like clefts and slits. It can be benign or locally malignant. Occasionally it may be frankly malignant. 15% may metastasize to distant sites.

It distorts the breast and may lead to ulceration of the overlying skin. It may present as a fungating lesion.

Microscopically it is more cellular than other fibroadenomas and there is myxomatous change in the fibrous tissue. It shows increased stromal cellularity, anaplasia and high mitotic activity.

Malignant change can occur rarely. Lymph node metastasis is rare as in other sarcomas. It was previously called cystosarcoma phylloides.

This should be removed very carefully otherwise recurrence can occur.

LIPOMA

It is collection of discrete area of fat in the breast. It can be easily diagnosed clinically. Treatment is surgical excision.

PLASMA CELL MASTITIS (RARE)

It is a rare condition of breast showing lumpyness.

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round and firm lump or lumps. It is more common in obese female with large size breast.

It is due to localized disruption of fat cells following trauma. The fat in saponified slowly by the blood and tissue lipases. This is followed by fibroblast and macrophage reaction leading to localized hard irregular lump in the breast fat.

Necrosis of fat occurs in the breast tissue. There may be foci of hemorrhage in the beginning but later on there is liquefactive necrosis.

Mammography must be interpreted very carefully.

FNAC and trucut needle or excision biopsy are confirmatory for the diagnosis.

TUBERCULOSIS (RARE).

It may present as a breast lump, cold abscess or a solitary sinus or multiple discharging sinuses. History of contact with tuberculous patient is asked. Standard anti-tuberculous chemotherapy offers good results. Surgery is reserved for residual lumps or resistant disease.

MALIGNANT SWELLINGS

(CARCINOMA BREAST)

Carcinoma of the breast is not so rare in Pakistan as it is thought. A hard lump in the breast with irregular surface could be a malignant lump.

It can be mobile or adherent to the underlying muscle or overlying skin. It may be associated with enlargement of regional lymph glands.

All such lesions should have FNAC, trucut needle biopsy or excision biopsy. Further management should be done according to the histopathological picture.

Sarcoma (rare)
Lymphoma (rare)

Associated diseases

Retro mammary abscess (TB)
Chondroma of chest wall
Deformities of ribs
Mondor's disease
Sebaceous cyst over breast

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Fig-8.1 Giant fibroadenoma breast
(Courtesy Sajid Shiekh, FCPS)

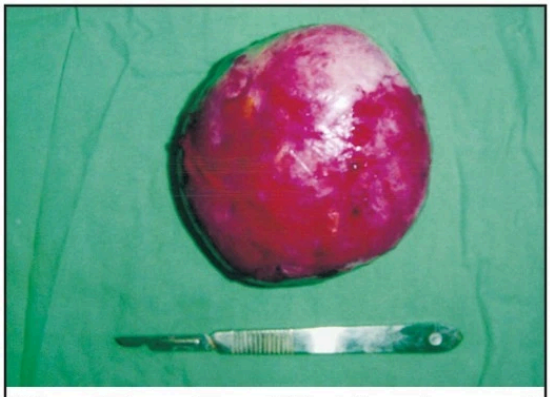

Fig-8.2 Operated specimen of Giant fibroadenoma of breast
Courtesy Sajid Shiekh, FCPS

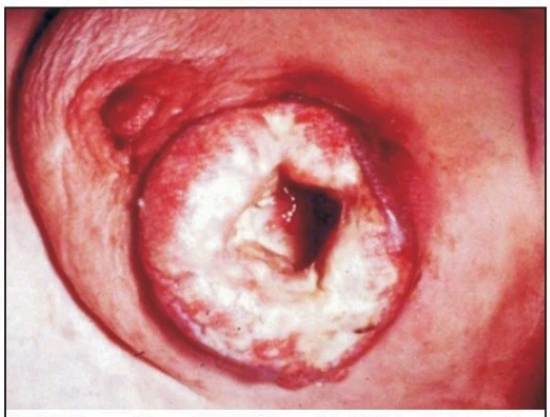

Fig-8.3 Fungating lump breast (Carcinoma breast)

Fig-8.4 Breast lump with nipple retraction

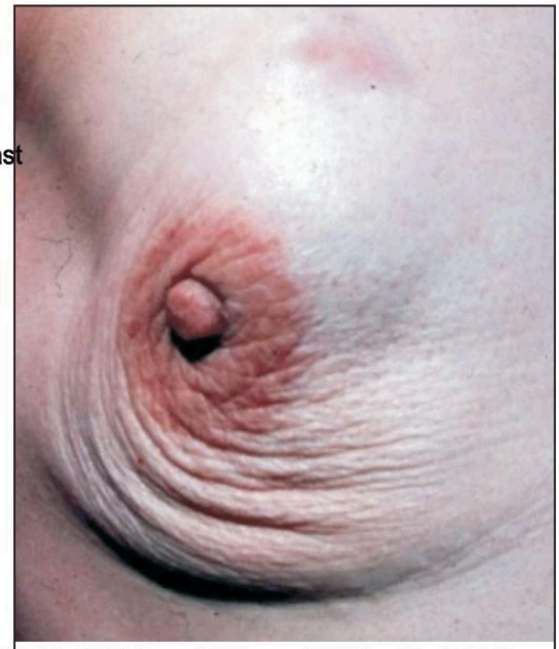

Fig-8.5 Breast lump with nipple distortion

Fig-8.6 Lump in the left axilla arising from the breast
Courtesy Sajid Shiekh, FCPS

Fig-8.8 Breast lump with nipple inversion

Fig-8.7 Cystosarcoma phylloides right breast

Fig-8.9 Breast lump (Carcinoma breast)

Fig-8.10 Breast lump (Giant fibroadenoma left breast)

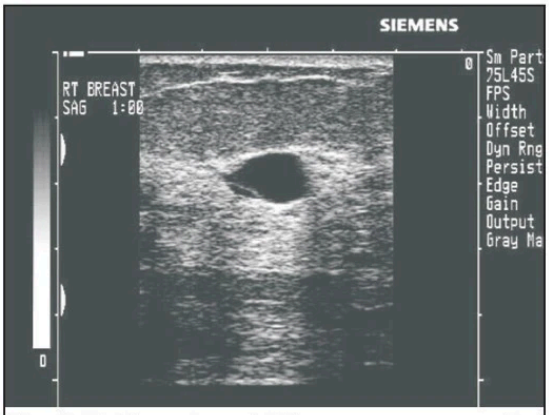

Fig-8.11 Breast cyst (Sonomammography)

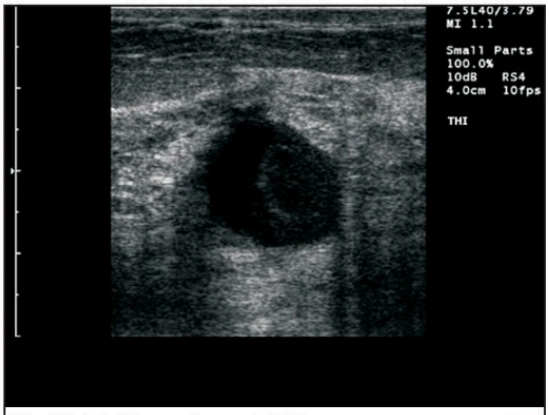

Fig-8.14 Breast cyst (Sonomammography)

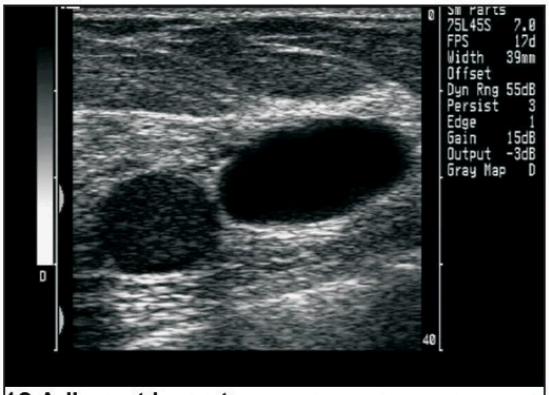

Fig-8.12 Adjacent breast masses on sonomammography. (A debris filled cyst and a simple cyst)

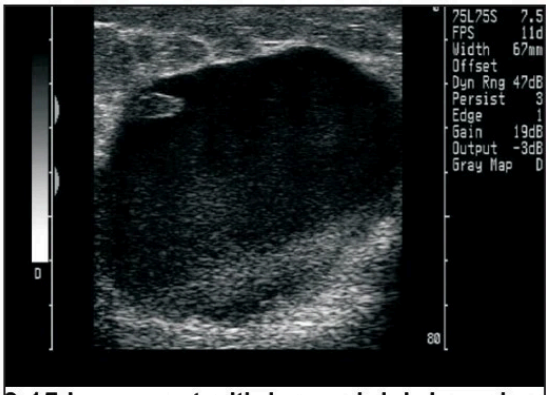

Fig-8.15 Large cyst with layered debris and a solid component. (Sonomammography)

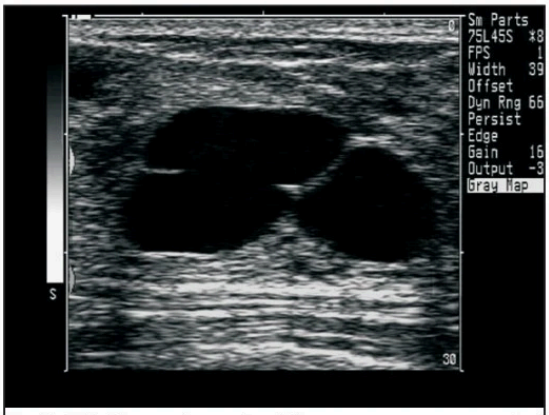

Fig-8.13 Breast cysts (Sonomammography).

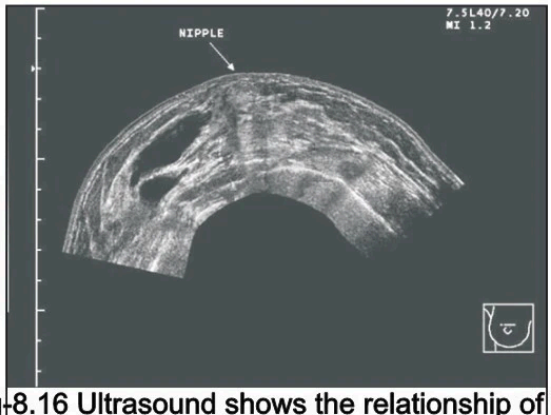

Fig-8.16 Ultrasound shows the relationship of the dominant cyst to other masses in this patient.

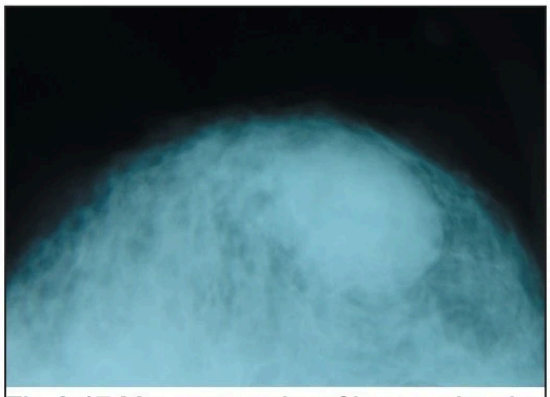

Fig-8.17 Mammography of breast showing fibroadenoma of left breast.

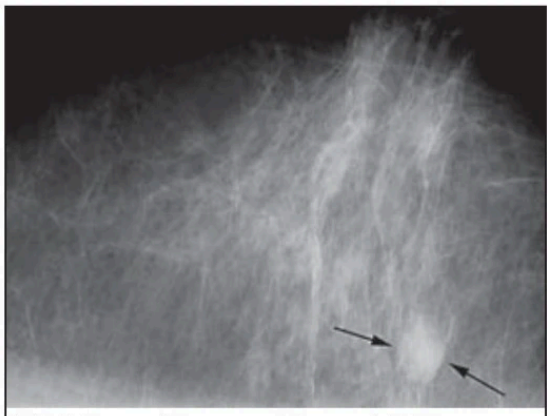

Fig-8.20 Fibroadenoma of breast (Mammography)

Fig.8.18 26 years old lady with left breast lump fibroadenoma (Mammography)

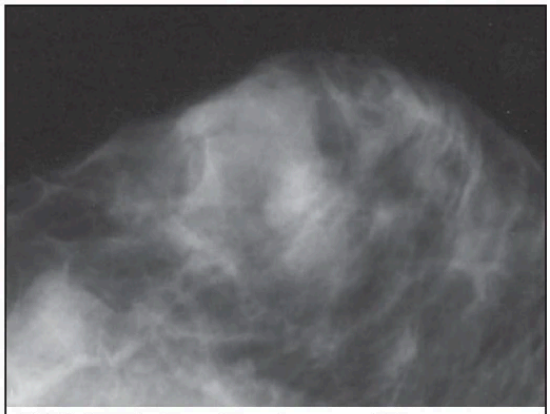

Fig-8.21 Medullary Carcinoma (Mammography)

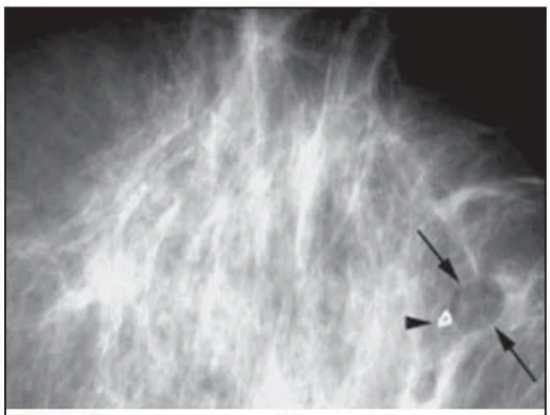

Fig-8.19 Fibroadenoma of breast (Mammography)

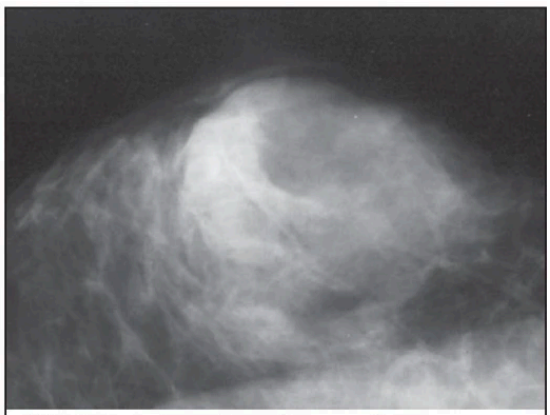

Fig-8.22 Medullary Carcinoma (Mammography)

Chapter-09

Presentation of Breast Diseases - 2
Breast Pain

Objectives

- To be able to diagnose breast pain.
- To be able to differentiate between various causes of breast pain.
- To be able to find out the cause of breast pain.
- To be able to manage breast pain properly.

PRESENTATION OF BREAST DISEASES -2
BREAST PAIN

Shuja Tahir, FRCS, FCPS
Abid Bashir, FCPS

MASTALGIA

Mastalgia or Mastodynia can be defined as “breast pain of sufficient severity for a women to seek medical advice”. Some breast pain or discomfort is experienced by about 2/3rd of women during the premenstrual phase. It may be associated with increased nodularity[1]. This pain is mild, lasts for a short time in the premenstrual phase but more important, it resolves with menstruation. It can be considered with in the spectrum of “normal”.

The development of severe pain and nodularity which may last for most of the menstrual cycle is considered as abnormal and may interfere significantly with patient’s everyday activity. Although two third women have some premenstrual discom-fort, about half of them have severe pain, enough to consult health care provider. Effect of this severe pain on sexual, physical, social and school /workplace activities has been observed to be 37%, 12% and 8% respectively[2].

Mastalgia is also a major cause for increased use of mammography (2.2 to 4.7 times) in younger women below the age of 35 years [2,3].

ETIOLOGY & PATHO-PHYSIOLOGY

The underlying cause of severe mastalgia remains unknown. The traditional surgical view, that pain in the breast is largely an expression of psychoneurosis was dismissed in the late 70s by Preece et al[4]. Similarly theory of increased water retention in patients with mastalgia is also disproved[5]. Inflammation, as a cause of pain has also been postulated but Ramakrishnan et al. compared expression of three inflammatory mediators (IL-6, TNF-α and IL-1α) in tissues from painful and normal breasts. Even slightly lower levels of IL-6 and TNF-α were found in tissues from painful breasts. Specimens were also examined for evidence of inflammatory infiltrate, but no identifiable histological correlation was found[6].

Recently duct ectasia has been described as a major factor associated with mastalgia. Ultrasonography was used in mastalgia patients to investigate morphological structure and

postulated in causation of mastalgia for long time. Recently smoking, caffeine and perceived stress has been shown to be associated with mastalgia (O.R = 1.52, 1.53 and 1.7 respectively)[2].

Markedly increased levels of gonadotropin hormones throughout the cycle has also been observed in patients with mastalgia[8]. [the use of gonadotropin inhibitors may be trailed in mastalgia patients). These studies have shown interesting results but merit further investigations.

CLASSIFICATION

Classification of mastalgia has also been confusing and unsatisfactory. It is usually classified into two groups. Cyclic and non cyclic mastalgia[9]. Cyclic mastalgia account for 67% of cases, usually bilateral, (although may be unilateral) varies during menstrual cycle and is typically worse in the luteal phase. It is relieved on the onset of menopause. Non cyclic pain accounts for the remaining 33%, being further divided into true non cyclic pain and chest wall pain.

The other classification[10] based on etiology is as follows;

Cyclic Mastalgia: Cyclic mastalgia is so called since patient has obvious menstrual cycle related pattern i.e. pain increases and decreases with menstrual cycle, maximum being during luteal phase.

It is often associated with palpable nodularity. It is bilateral in 50% patients. It is also poorly localized and usually involves upper and outer quadrant, 50% may radiate but usually are confined to breast tissue

Trigger Point Pain: There is no cyclic variation. Usually well localized, it may be precipitated or increased by touch. It is rarely bilateral, 50% radiate usually to sub areolar part and inner quadrant. It may have severe burning abscess like exacerbations. Trigger point pain has a strong association with clinical, radiological and histopathological features of duct ectasia/periductal mastitis complex of disorders; past or present.

Tietze's syndrome: It is the painful, swollen and tender costo-chondral junction, usually of the 2nd rib. Because of the vicinity of the female breast to the area, pain may be perceived as breast pain.

Previous trauma: The breast may have had abscess, biopsy or injury. The scar albeit deep in the breast with no cutaneous component can become a source of pain many years after the initiating injury. Similarly skin incision specially if across hair lines, may be a source of pain.

Sclerosing adenitis: It is a benign condition and usually is histopathology of mammographically defined

start of **oral contraceptives.**

Fat necrosis, thrombo phlebitis of the vessels of the lateral chest wall (Mondor's disease), and tuberculosis are causes of breast pain occasionally.

The pathognomonic sign of Mondors's disease is guttering of the superficial veins of the breast.

Tuberculosis presents either as an abscess or like a malignant tumor, poorly demarcated and with skin attachment.

Fat necrosis may mimic cancer clinically and radiologically.

Referred Pain: The pain may be referred from intrathoracic or intra abdominal inflammation to the breast e.g. pain of cholecystitis or pleurisy.

Idiopathic: The origin of breast pain remains obscure in some patients, although the majority of patients fall into one of the categories described above.

CLINICAL EVALUATION & MANAGEMENT

The main stay of evaluation is triple assessment. The aims are;

To differentiate between cyclic and non cyclic mastalgia.
To find out if there is any underlying pathology.
To rule out malignancy.

History of pain should include onset, duration, character, severity, site, localization, radiation progression, cyclic changes, relieving and aggravating factors.
The systemic enquiry should be performed to rule out causes of referred pain. History of dietary habits, smoking, behavior, stress and tension, occupation and previous surgery should also be sought.

Thorough examination of both breasts is performed in a systematic order. Tenderness and/or any localized tender spot, nodularity or discrete lump is sought carefully. Condition of the nipple and any discharge is noted. Previous scar if any is properly assessed. Both axillae are examined. Systemic examination to find out intra-thoracic, intra-abdominal and chest wall pathology is also performed.

Mammography and/or FNAC is advised wherever indicated.

Once malignancy is ruled out, patient is reassured. Carcinoma breast is less likely to be a diagnosis in a woman with breast pain as compared to women who do not complain of breast pain regardless of age and other breast cancer risk factors[11]. It has also been noted that majority of these patients respond to simple reassurance and explanation[1].

If any other obvious pathology is found, it is treated on its own merit. Simple

helpful in most of the patients[12]. Relief of pain is seen in 58% patients but 42% patients shows adverse effects. Active breast movement on weak suspensory ligaments may contribute considerably to mastalgia. Good external support by supportive brassiere can relieve most of patients' symptoms.

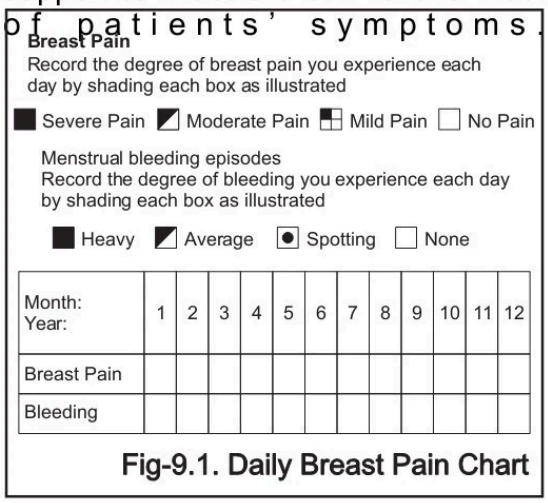

Fig-9.1. Daily Breast Pain Chart

Table-1. Cardiff breast pain score (CBS)

CBS I	An excellent response leaving no residual pain
CBS II	A substantial response leaving some residual pain but considered by patient to be easily bearable
CBS III	A poor response leaving substantial residual pain
CBS IV	No response

The patient is reviewed after two months. Pattern of pain is assessed and response is graded according to Cardiff Breast Pain Score (Table-1).

Specific drug treatment is considered which is balanced against the chance of response to treatment and risk of side effects. Patient is reviewed every two to three months. The decision regarding continuation or change of treatment is made according to patient's response. An algorithm for the treatment of mastalgia is given in Fig-9.2.

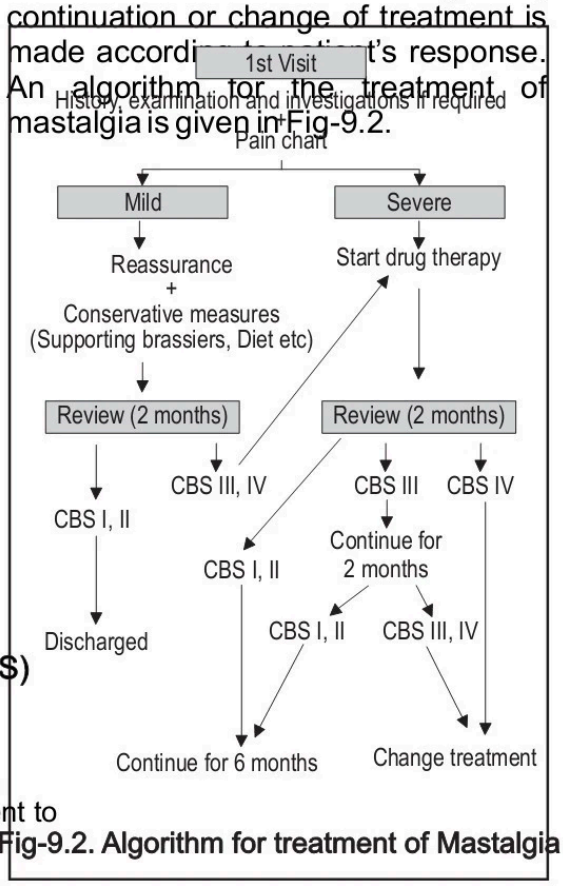

Fig-9.2. Algorithm for treatment of Mastalgia

DRUG THERAPY

EVENING PRIMROSE OIL

Evening primrose (Oenothera biennis L) is a North American wild flower that has escaped cultivation and is now

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long history among native Americans and was transferred to Europe by colonial settlers[13].

The oil expressed from plant's small dark seeds is rich in essential fatty acids: approximately 65% Linoleic acid and 8% to 10% gamma linolenic acid[14]. These constituents are precursors in the manufacturing of prostaglandin E_1 one of the anti-inflammatory prostaglandins. Women with mastalgia have abnormal fatty acid profile and decreased levels of linolenic acid metabolites[15].

Treatment with evening primrose oil improves essential fatty acid profile to normal[16]. Although, it may take upto three months to provide relief of symptoms, its effectiveness has been proved in placebo controlled trial with overall response rate of 45% in cyclic mastalgia and 27% in non cyclic mastalgia with fewer side effects (2% for evening primrose oil versus 22% with danazol and 33% with bromocriptine)[17,18].

Evening primrose oil is used as a first line treatment for cyclical mastalgia[19,20,21]. In a recent survey 13% to 20% British surgeons recommended evening primrose oil for this use[22]. Patients with severe premenstrual symptom rate evening primrose oil as one of the most effective treatment they had ever used[23]. Evening primrose oil is particularly useful in younger women who may require long term therapy, who wish to avoid anti-hormonal therapy and remain on oral contraceptive. Addition of an anti oxidant (vitamin E) might improve the efficacy of evening primrose oil treatment by reducing its metabolism via lipid peroxidation[3]. The dose is 2 capsules TDS(2-4gm/day standardizing to 9% gamma linolenic acid) and it should be given for at least 3 months. To obtain full benefit from this regimen it may be necessary to ensure adequate levels of vitamin B1, B6 and Zinc which are co-factors in the proposed metabolic pathway along with vitamin C[10].

Comparable results has been seen of fish oil, Corn oil and corn oil with wheat germ oil with those of evening primrose oil for mastalgia[24].

DANAZOL

Danazol is a gonadotrophin release inhibitor. It remains the most effective first and second line treatment with its effectiveness confirmed in controlled trials[25,26]. A useful response to treatment is observed in 70% of patients with cyclic mastalgia and 31% with non cyclic mastalgia[25]

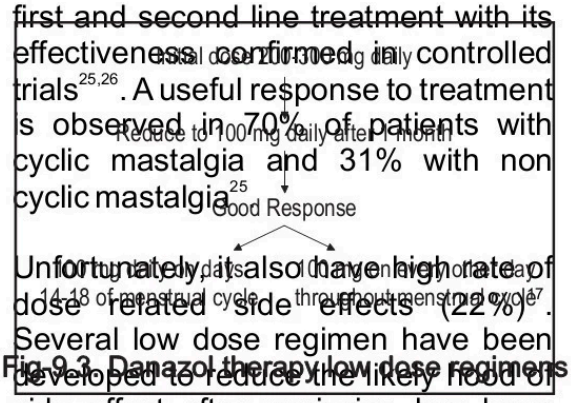

Fig-9.3. Danazol therapy low dose regimens

Unfortunately it also have high rate of dose related side effects (22%)[27]. Several low dose regimen have been developed to reduce the likely hood of side effect after remission has been induced with a full dose of 200 mg daily[27, 28] (Fig-9.3). These regimens may also be used in patients who relapse

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therefore, adequate contraceptive precautions are required.

BROMOCRIPTINE

Bromocriptine is dopamine agonist which has been successfully used for many years to treat mastalgia. It has been shown to decrease serum prolactin levels in normal and hyperprolactinemic women. Its effectiveness has been confirmed in several single center controlled trials[29,30] and a large European multicentre study[31].

Clinical improvement is observed in 47% of patients with cyclic mastalgia and 20% with non cyclic mastalgia.

The side effect profile is the limiting factor for the more extensive use of this treatment option. Reported side effects include nausea, vomiting, headache, dizziness and fatigue all of which are dose related. To minimize these side effective, an incremental dosing regimen is proposed starting with 1.25 mg at bedtime, increasing by 1.25 mg every three to four days until the full dose of 2.5 mg twice daily is reached. Treatment should be continued for 3-6 months.

TAMOXIFEN

Tamoxifen an anti oestrogen, has many uses in the management of breast disorders. Its effectiveness in the treatment of breast pain has been proven in several clinical trials[32,33]. A lower dose of 10 mg daily has been shown to be as effective in the treatment of mastalgia with a significantly reduced side effects compared with 20 mg daily[34]. The dosage is tailored to individual patient requirement and symptom control balanced against troublesome side effects. Better response is observed in patients with cyclic mastalgia than in those with non cyclic mastalgia. Although yet not licensed for mastalgia treatment in United States, it is used as 2nd or 3rd line treatment.

GOSERLINE

Goserline, LHRH analogue has shown to be effective in both cyclic and non cyclic mastalgia refractory to first line therapy[35]. It induces reversible ovarian suppression with castrate levels of ovarian hormones being attained within 72 hours[36]. Adverse effects (principally hot flushes) are common and monthly subcutaneous injections does have compliance problem. It should, therefore, be reserved for those patients who fail to respond to other forms of treatment. It may be used to induce a rapid relief of symptoms to be followed by other therapies as maintenance.

MISCELLANEOUS

Lisuride maleate, one tablet of 0.2 mg daily for two months has shown to significantly reduce prolactin level, and

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bilateral. Sometimes it becomes very difficult to differentiate between various causes of breast pain.

Following conditions present with unilateral or bilateral breast pain. These can be diagnosed by triple assessment and treated effectively.

- Mastalgia.
- Pregnancy.
- Menstruation (cyclical mastalgia).
- Onset of puberty.
- Lactation.
- Cracked nipple.
- Inflammation of nipple.
- Breast cyst.
- Galactocele.
- Breast abscess.
- Sub-mammary abscess.
- Mastitis, acute mastitis, periductal mastitis.
- Epitheliosis of nipple.
- T B breast.
- Post traumatic.
- Anxiety.
- Angina.
- Pain from ribs under the breast.
- Cervical spondylosis.
- Herpes zoster.

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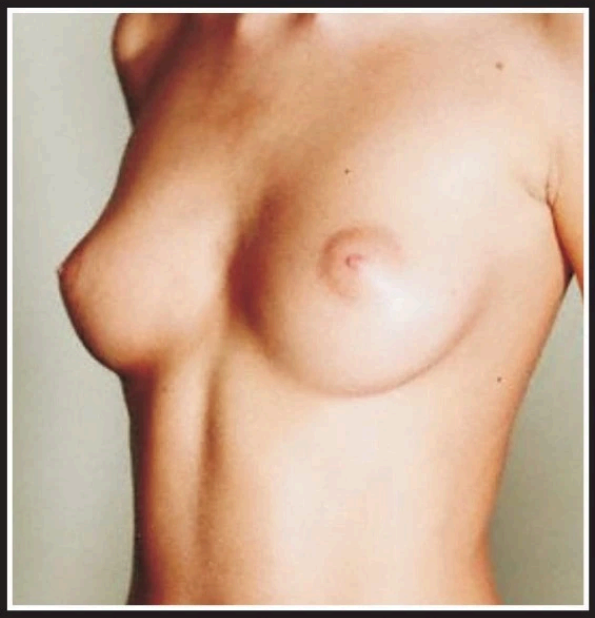
Chapter-10

Presentation of Breast Diseases - 3
Nipple Problems



Objectives

- To diagnose the problem at the earliest.
- To rule out malignancy.
- To find out the cause of problem.
- To investigate the problem.
- To treat the problem adequately.
- To monitor the effects of treatment during

PRESENTATION OF BREAST DISEASES - 3
NIPPLE PROBLEMS

Shuja Tahir, FRCS, FCPS
Tariq Mehmood, FCPS

NIPPLE PROBLEMS

These are the problems/diseases related to nipple areola complex.

CONGENITAL

- Absence.
- Supernumery.
- Bifid.
- Inversion.

ACQUIRED

- Inversion.
- Plasma cell mastitis.
- Mammary duct fistula.
- Duct ectasia.
- Retroaerolar carcinoma.
- Paget's disease.
- Amazia, Amastia

Complete absence of the breast and nipple is rare. It may be associated with failure of development of pectoralis muscles (Poland's syndrome).

SUPERNUMERY NIPPLE

It is the presence of extra nipple present in the mammary line. It is neither a common abnormality nor has any significance. It doesn't need any treatment either.
The breasts are modified sweat glands and are derived from ectodermal mammary ridge, which extends from axilla to groin region.

In many animals breasts develop along the whole length of this ridge, but in human only a pair develop in the pectoral region. Sometimes supernumery or only nipple may be seen along this line[10].

BIFID NIPPLE

The nipple is divided into two parts usually from the middle congenitally. The nipple may be inverted or normal. It is usually associated with recurrent infection. It is rare but well defined entity. No treatment is required. The patient is reassured.

INVERSION OF NIPPLE

Inversion of nipple is a condition which is chara-cterized by inward displacement of the tip of nipple. It leads to appearance of a slit like opening and disappearance of almost whole of the nipple.

Congenital failure to protrude nipple is also called inversion. Incidence of inversion is quite high. About 20% of females present with this problem. They should be reassured. These patients mostly need no treatment. Sometime they present with the difficulty is suckling by the baby. Nipple sheath is applied to the nipple for helping the baby to suck easily. It also helps to get the nipple everted.

Acquired inversion of nipple is mostly due to duct ectasia, plasma cell mastitis or any other inflammatory lesion. Retro areolar carcinoma may also lead to inversion of nipple.

MAMMARY DUCT FISTULA

Mammary duct fistula is an aftermaths of periductal mastitis. It presents as a discharging sinus around the areolar margin.

DUCT ECTASIA / PLASMA CELL MASTITIS /
PERIDUCTAL MASTITIS

This is a common disease process. Its etiology is not known. It is not clear whether ectasia or inflammation is the primary problem. No one is clear which starts first. Sloughing of ducts initiates a process of periductal mastitis. Clinical features follow the pathological changes.

The terminal lactiferous ducts enlarge in size and then dilate grossly. The epithelial lining disintege-rates and plugs the dilated lactiferous ducts.

Multicolored fluid from the nipple is discharged. Periductal chemical mastitis starts. It is infiltrated with plasma cells and Foreign Body Giant cells.

A hard indurated mass with overlying inflammation may appear at the areolar margin.

This inflammation may resolve automatically or change into periareolar abscess. If it is not treated adequately it may lead to mammary duct fistula. The repeated episodes of periductal mastitis leads to fibrosis along ducts which shrink and may lead to inversion of nipple.

It is commonly seen in postmenopausal women but it may occur in premenopausal women. It is often bilateral and multiple abscesses and fistulae may be seen.

Treatment is surgery.

PAGET'S DISEASE OF BREAST

Paget's disease is macroscopic superficial skin manifestation of underlying carcinoma of breast. Usually it presents as a unilateral nipple ulceration. Sometimes whole of nipple is eroded and it comple-tely disappears. The cancer of breast becomes evident sooner or later if it is

areola complex.

Paget's disease of breast is a type of ductal carcinoma which extends from the ducts to involve the skin of nipple and areola. The malignant invasion of the nipple presents as eczematous change of unilateral nipple and areola. It many present as an encrusted and scaby tumor present at nipple and areola.

The involved skin is ulcerated, fissured and oozing. It may have surrounding area of inflammatory hyperaemia and edema. Advanced cases show total ulceration or even loss of nipple and areola. There may be superimposed infection and suppurative necrosis. Its symptoms include tenderness, itching, burning and intermittent nipple discharge.

The underlying mass or lump in rarely palpable.

The epidermis is involved by the malignant cells and these are called. "Pagets cells". Their origin and nature is unknown. The intraductal lesion is often multifocal and ducts throughout breast may be dilated due to obstruction of central collecting ducts at the ampula.

Paget's cells are large, anaplastic and hyper-chromatic ovoid cells surrounded by a clear zone or halo. These have pale cytoplasm. It is possibly due to ballooning degeneration. The anaplastic tumor cells lie singly or in clusters within the epidermis.

NIPPLE RETRACTION

It is the inward displacement of whole/part of nipple from its base in the direction of disease process. It is usually due to malignancy. The lesion may be present in the breast tissue at any part. The retraction is due to involvement of connective tissue Bands (ligaments of Astley Cooper).

It is acquired problem which could be due to duct ectazia, carcinoma or surgical problem. All these problems are discussed at length, at some other part of the book.

NIPPLE DISCHARGE

Nipple Discharge is a complex diagnostic challenge for clinicians. A variety of diseases, such as intraductal papillomas, mammary duct ectazia, breast cancer, pituitary adenomas, breast absce-sses and infections can manifest as nipple dis-charge[1].

Nipple discharge disorders is a field in which there has been both increasing awareness on part of patients and advancements in management.

The nipple discharge can be classified according to its color, cellularity and biology. The discharge has to be true, spontaneous, persistent and non lactational to be significant[3].

- Pus discharge.

CAUSES OF NIPPLE DISCHARGE

LACTATION = Physiological

GALACTORRHOEA

It is the discharge of milk from nipple which is unrelated to breast feeding or lactation. It can be physiological after cessation of feeding but continuous mechanical stimulus to nipple promotes milk discharge.

1. Physiological discharge after cessation of lactation.
2. Drug related.

a. Drugs which reduce production of prolactin
Dopamine.
Trycyclic antidepressants.
Methyl dopa.
Cimetidine.
Benzodiazipine.
B. Dugs which block dopamine receptors.
Phenothiazide.
Metachlopramide.
Hexachlopramide.
Heloperidol.
c. Oestrogen.
Digitalis.

3. S P O N T A N E O U S GALACTORRHEA

Pituitary adenoma producing prolactin
Broncho-genic carcinoma.
Cushing's syndrome
Hypothyroidism

LACTATION

This is the most common cause of nipple discharge and needs no treatment. This is physiological and milk discharge usually stops after cessation of breast feeding. In parous women milk can be expressed out even after two years of cessation of lactation.

Some times pregnant patient can have blood stained discharge which settles on its own. Occasionally neonates may show milk discharge from their nipple if luteal or placental hormones get entry into fetal circulation again it needs no treatment.

PATHOLOGICAL

Intraductal papilloma
Duct ectazia
Carcinoma
Fibrocystic disease
Trauma
Infection

B L O O D S T A I N E D N I P P L E DISCHARGE

It causes high degree of anxiety in women because of fear of breast cancer. Most frequently it is benign. It is commonly caused by intra ductal papilloma, duct ectasia and less frequently by carcinoma breast[2].

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Discharge may be from peri areolar breast skin. Which may occur due to different skin diseases like eczema, psoriasis or chancre. Peri areolar discharge can also be seen in Paget's disease and duct ectasia.

PATHOLOGICAL NIPPLE DISCHARGE

It is usually spontaneous, unilateral and single duct involvement is seen. The discharge may be serous, serosanguis or blood stained.

TRIPLE ASSESSMENT

Correct diagnosis requires triple assessment. Appropriate planning of management is done after assessment of the patient and understanding of disease process.

CLINICAL EXAMINATION

A detailed clinical evaluation by triple assessment is invaluable to determine the pathophysiology and assess risk of malignancy[1].

Both breasts and axillae are examined. Nipple is cleaned and breast is squeezed to see nature and site of discharge and number of ducts involved.

Hemoccult Test is performed to confirm presence of blood in the discharge. Galactography, ultrasound examination, exfoliative cytology are useful[2].

A large number of false negative results make these tests less productive and histopathological tests are required to confirm the diagnosis[2].

SERUM PROLACTIN LEVEL

When all other investigations are normal and patient has got amenorrhoea along with visual disturbances, then raised serum prolactin level may suggest pituitary adenoma. Sometimes serum prolactin may rise in bronchogenic carcinoma.

IMMUNOLOGICAL TESTS

Modern immunological tests can be performed on cytology smears where occurrence of high levels of carcino-embryonic antigen (CEA) could indicate latent malignancy[3].

IMAGING

ULTRASOUND EXAMINATION OF BREAST (SONOMAMMOGRAPHY)

High resolution ultrasound is helpful in visualizing intra ductal abnormality and are becoming a good complimentary approach if not an alternative to traditional radiology techniques[3].

Ultrasound is more sensitive than galactography in cancer diagnosis. It also permits guided biopsy and pre operative localization of impalpable

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DUCTOGRAM (GALACTOGRAPHY)

Galactography is the state of art approach to investigate patients with nipple discharge disorder and this examination can demonstrate the size, location and extent of an intra ductal abnormality[3].

It may be helpful in diagnosing intra duct papilloma.

MR galactography has been shown to be of diagnostic value but not as informative as radio-galactography[3].

FIBROPTIC DUCTOSCOPY

Early success of image guided excision of papilloma and duct endoscopy promise a significant improvement in diagnostic accuracy through minimally invasive procedure.

The most sophisticated investigation method which can be used therapeutically as well is fibroptic ductoscopy of the concerned duct in a breast.

It is a new technique and is expensive. It is a fascinating and promising approach for visualizing the intra ductal lumina[3].

Mammary ductoscopy for pathological nipple discharge is a safe, effective procedure that offers advantages of high lesion localization rate and intra operative guidance, therefore, negating the need for pre-operative ductogram. Lesions deep within the ductal system can be identified and removed which could have been missed by blind duct excision[5].

It can be helpful to pick up cells for cytology. Its role is yet controversial

CYTOLOGICAL EXAMINATION

Discharge is examined under the microscope to rule out malignancy but false negative reports may confuse the management plan. Ductal lavages in combination with cytology provide promising results[2].

Cytology smears of discharge material have helped to classify the cellular material, providing information about normality, atypia and malignancy and also about papillary formation[3].

MANAGEMENT

Objectives of treatment are to;

1. To rule out malignancy.
2. To reassure the patient.
3. To offer definitive treatment of the causative factors

SURGERY

Indications of surgery;

a. Single duct discharge

   i. Blood stained discharge
   ii. Mammography shows

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The patients with nipple discharge should be clearly differentiated from those who require surgery and who don't need it. Surgically significant nipple discharges are watery, serous (yellow), serosanguis or blood stained[3].

Women presenting with pathologic nipple discharge require duct exploration regardless of cytologic or radiologic findings. When discharge is the result of local extensiveness of disease and intra ductal spread, it may preclude breast conservation in more than 60% of cases[4].

Nipple discharge in males is very rare but once it is there, it should be regarded with suspicion. There are high chances of underlying malignancy. Surgical excision of the involved ductal system from which the discharge emanate. It is the only reliable procedure in establishing a certain diagnosis and controlling the blood stained discharge[2].

Histologically it is an extension of intra ductal carcinoma or even infiltrating ductal carcinoma. 30-40% of these patients have metastasis at the time of surgery and prognosis is less favorable than simple intra ductal carcinoma which is diagnosed at earlier stage.

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Fig-10.1 Accessory nipple
Courtesy Prof. Asif Zafar

Fig-10.4 Blood stained nipple discharge.

Fig-10.2 Accessory nipple male breast

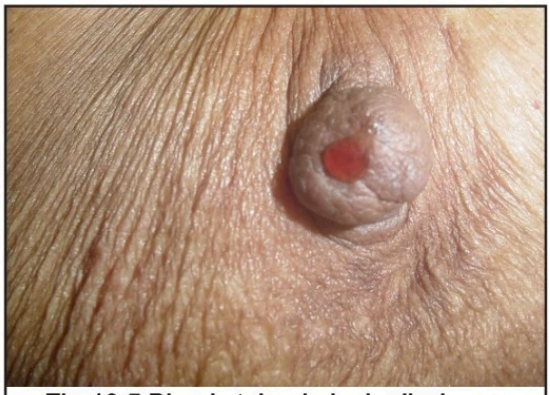


Fig-10.5 Blood stained nipple discharge
Courtesy Sajid Shiekh, FCPS

Fig-10.3 Lactating breast showing milky and blood stained discharge.

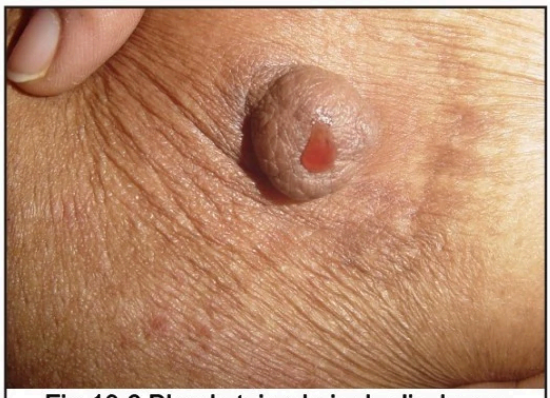


Fig-10.6 Blood stained nipple discharge
Sajid Shiekh, FCPS

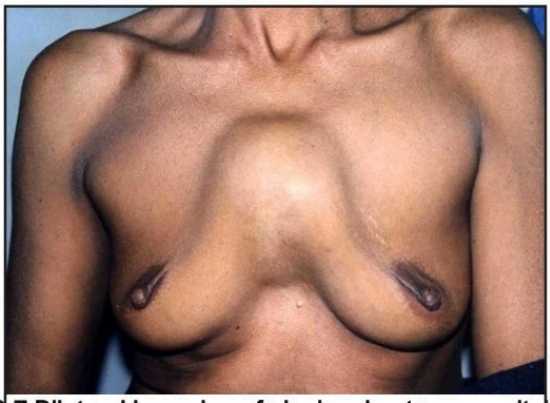


Fig-10.7 Bilateral inversion of nipples due to congenital chest deformity. Courtesy Faisal Bilal Lodhi, FCPS

Fig-10.10 Paget's disease of nipple.

Fig-10.8 Partial retraction of nipple (Inflammato

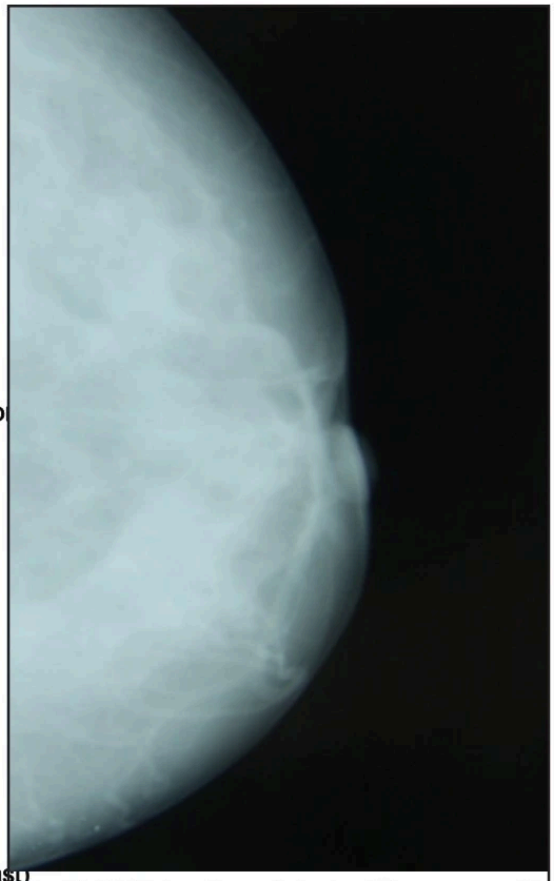


Fig-10.9 Nipple retraction with Peau-de-Orange (Cancer Breast) Courtesy Sajid Shiekh, FCPS

Fig-10.11 Retraction of nipple (Mammographic appearance

Fig-10.12 Paget's disease of nipple
Courtesy Sajid Shiekh, FCPS

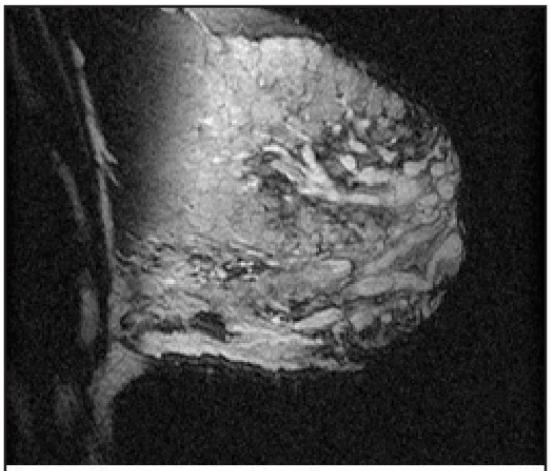


Fig-10.13 Ductography of lactating breast.

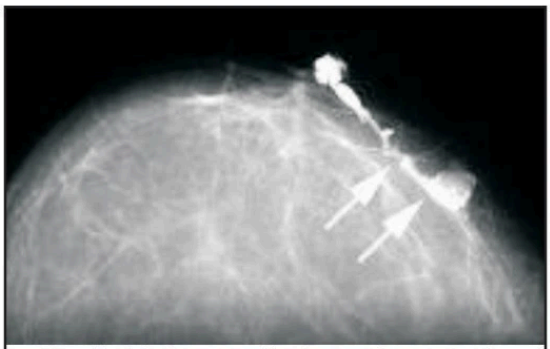


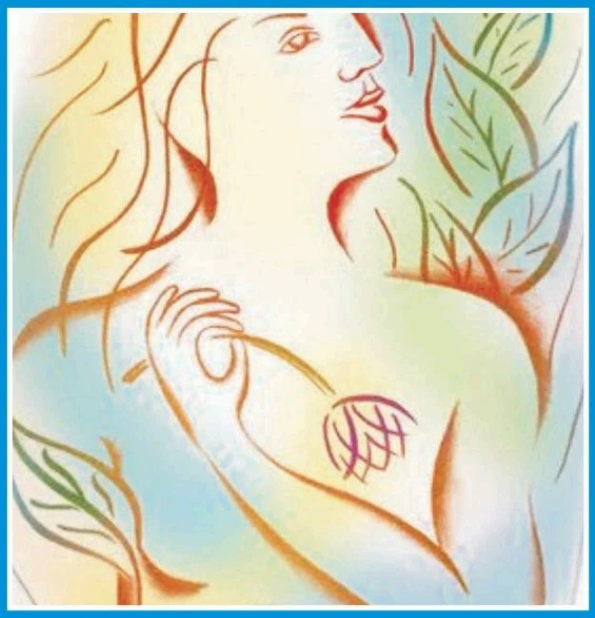
Fig-10.14 Serous discharge from nipple.
(Ductography)

Fig-10.15 Paget's disease of nipple with early distortion.

Fig-10.16 Serosanguis discharge from nipple
(Ductography)

Chapter-11

Benign Diseases of Breast



Objectives

- To diagnose benign conditions and rule out malignant disease.
- To find out the nature of benign disease. (Inflammatory, ANDI, Malignancy).
- To plan investigations effectively.
- To plan effective management.

BENIGN **DISEASES** OF BREAST

Shuja Tahir, FRCS, FCPS
Abid Bashir, FCPS
Ata ul Latif, FCPS

The breast is a physiologically dynamic organ in which cyclical variations are superimposed on changes of development and involution throughout woman's life[1].

Immature breast is composed mainly of dense fibrous tissue stroma and scattered epithelial lined ducts. There is an increased deposition of fat at puberty giving the pair of breast a shape and women the sense of feminity [2,3].

New ducts are formed by a process of elongation and lobular units appear, terminal end buds arise from pleuripotent stem cells in the immature ducts. Growth of breast is controlled by many hormones;

1. Oestrogen.
2. Progesterone.
3. Pituitary hormones.
4. Insulin.
5. Thyroxine.

Growth hormone seems to be responsible for the terminal end duct development via production of insulin like growth factor – 1 (IGF-1).

Most of the patients presenting with breast problems have benign condition (over 90% of patients).

Accurate classification of benign breast diseases depend on relationship between normal breast morphology and the changes that occur throughout a woman's reproductive life from breast develop-ment through cyclical change to changes during pregnancy and lactation, eventually involution.

The quality of investigations and understanding of breast problems has improved over recent years. Patients demand investigations and treatment for symptoms. There is question of pre-malignant conditions.

Screening programs present pathologists and clinicians as yet ill-defined clinical entities.

The concept first proposed by Hughes in 1982 has been called Aberrations of Normal Development and Involution (ANDI) The concept implies that most benign disorders can be regarded as mere aberrations of normal processes[3].

Classification of the pathogenesis of non malignant breast disease based on the concept of Aberration of Normal Development and Involution (ANDI)			
Physiological state of the breast	Normal	Benign disorder	Benign disease
Development	Duct development, lobular development, stromal development	Nipple inversion Fibroadenoma, Adolescent hypertrophy	Mammary fistula, Giant fibroadenoma
Cyclical Change	Hormonal activity Epithelial activity	Mastalgia and nodularity Benign papilloma	
Pregnancy and lactation	Epithelial hyperplasia Lactation	Blood stained discharge Galactocele	Peri-ductal mastitis with suppuration
Involution	Duct involution	Duct ectasia, nipple retraction	Lobular and ductal hyperplasia with atypia
	Lobular involution Involutional epithelial hyperplasia	Cysts, sclerosing adenosis Hyperplasia and micropapillomatosis	

contraceptive pill (hormonal).

PRESENTATIONS OF BENIGN BREAST PROBLEMS

BREAST PAIN (MASTALGIA)

All women old or young may feel pain in one or both breasts. It could be;

1. Cyclical.
2. Primary non-cyclical.
3. Musculo-skeletal.
4. Sclerosing adenosis.
5. Post-operative.
6. Cervical root pain.

BREAST LUMPS

1. Fibroadenoma.
2. Cyclical nodularity.
3. Cysts.
4. Galactocele.
5. Sclerosing adenosis.
6. Fat necrosis.
7. Lipoma.
8. Chronic abscess.
9. Normal structures (prominent rib, edge of previous breast biopsy, margin of breast tissue, etc).

NIPPLE & PERI AREOLAR REGION DISORDERS

1. Discharge.
2. Retraction.
3. Sepsis.

BREAST INFECTIONS

1. Lactational.
2. Non-Lactational.

OBJECTIVES OF ASSESSMENT

The objectives of evaluation of breast problems are;

- To confirm the diagnosis.
- To assess the extent of disease process.
- To form treatment plan.

These could be achieved by triple assessment (clinical examination, imaging and FNAC or core biopsy).

BREAST PAIN (MASTALGIA)

Mastalgia or mastodynia can be defined as "breast pain of sufficient severity for a women to seek medical advice".

Some breast pain or discomfort is experienced by about 2/3rd of women during the premenstrual phase. It may be associated with increased nodularity[1]. This pain is felt in the premenstrual phase but resolves with menstruation.

The development of severe pain and nodularity during the menstrual cycle is considered as abnormal and may interfere significantly with patient's everyday activity[2,3,4].

ETIOLOGY & PATHO-PHYSIOLOGY

The underlying cause of severe mastalgia remains unknown[5].

Inflammation as a cause of pain has also been postulated[6].

Recently duct ectasia has been described as a major factor associated with mastalgia. Ultrasonography was used in mastalgia patients to investigate the location of pain[7].

Hormonal and dietary factors have also been postulated in causation of mastalgia for long time. Recently smoking, caffeine and perceived stress has been shown to be associated with mastalgia[2].

Markedly increased levels of gonadotrophin hormones throughout the cycle has also been observed in patients with mastalgia[8]. Mastalgia is usually classified into following groups. Cyclic and non cyclic mastalgia[9].

This classification[10] is based on etiology and is as follows;

CYCLICAL MASTALGIA

Cyclic mastalgia is so called because patient has obvious menstrual cycle related pattern.

CYCLICAL NODULARITY

Usually complained by teenagers, lump varies in size with menstrual cycle and is located in upper outer quadrant.

If persistent FNAC is indicated with mammography in elderly. Younger

mastitis complex of disorders.

TIETZE'S SYNDROME

It is the painful, swollen, tender costo-chondral junction usually of the 2nd rib. Because of the vicinity of the female breast to the area pain may be perceived as breast pain.

PREVIOUS TRAUMA

The breast may have had abscess, biopsy or injury. Similarly skin incision may be a source of pain.

SCLEROSING ADENITIS

It is benign condition diagnosed on histopathology of suspicious lesion (microcalcifications)

CARCINOMA

Pain does not commonly accompany cancer in the breast. Mastalgia can still be the presenting symptom of operable breast cancer.

MISCELLANEOUS

Occasionally a fibroadenoma or cyst may be painful. Oral contraceptives, Fat necrosis, thrombo phlebitis of the vessels of the lateral chest wall (Mondor's disease) and tuberculosis are causes of breast pain.

The pain may be referred from intrathoracic or intra abdominal inflammation to the breast e.g. pain of cholecystitis or pleurisy.

IDIOPATHIC

The origin of breast pain remains obscure in some patients.

History of pain should include onset, duration, character, severity, site, localization, radiation progression, cyclic changes, relieving and aggravating factors. The systemic enquiry should be performed to rule out causes of referred pain. History of dietary habits, smoking, behavior, stress and tension, occupation and previous surgery should also be sought.

On local examination, thorough examination of both breasts should be performed in a systematic order. Tenderness and/or any localized tender spot, nodularity or discrete lump should be sought carefully. Condition of the nipple and any discharge should be noted. Previous scar if any should be properly assessed. Both axillae should be examined. Systemic examination to find out intra-thoracic, intra-abdominal and chest wall pathology should also be performed.

Mammography and/or FNAC should be advised wherever indicated.

Majority of these patients respond to simple reassurance and explanation[1].

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Use of supportive bra specially at night is also very helpful. Good external support by sports brassiere can also relieve most of patient's symptoms.

The patient should be reviewed after two months. Pattern of pain should be assessed and response should be graded according to Cardiff Breast Pain Score. Specific drug treatment should be considered which should be balanced against the chance of response to treatment and risk of side effects.

Patient should be reviewed every two to three months. The decision regarding continuation or change of treatment should be made according to patient's response.

Following drugs are used for treatment of mastalgia;

EVENING PRIMROSE OIL

Women with mastalgia have abnormal fatty acid profile and decreased levels of linolenic acid metabolites[15]. Treatment with evening primrose oil improves essential fatty acid profile to normal[8,9,10].

Anti oxidant (vitamin E) might improve the efficacy of evening primrose oil treatment by reducing its metabolism via lipid peroxidation[11,12,13,14,15].

DANAZOL

Danazol is a gonadotrophin release inhibitor. It remains the most effective second line treatment[9,13,14,15,16,28].

BROMOCRIPTINE

Bromocriptine is dopamine agonist which has been successfully used for many years to treat mastalgia. It has been shown to decrease serum prolactin levels in normal and hyperprolactinemic women. Its effectiveness has been confirmed[17,18,19,20,21].

TAMOXIFEN

Tamoxifen an anti oestrogen, has many uses in the management of breast disorders. Its effectiveness in the treatment of breast pain is documented [22,23,24].

GOSERLINE

Goserline, LHRH analogue has shown to be effective in both cyclic and non cyclic mastalgia refractory to first line therapy[25,26,27].

BENIGN BREAST LUMPS

Approximately 40% of the patients attending a breast clinic have a benign breast lump. The job of clinician is to define whether the lump is true abnormality and then to exclude malignancy. Enquiry into its duration, pain, change in size and relationship to menstrual cycle is important.

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years of age.

- It is common in black and oriental women.
- It commonly occurs in women under the age of 35 years.
- It constitutes about 75% of all the benign breast tumors.
- Occasionally it can be associated with lobular carcinoma.
- Approximately 25% of all discrete breast lesions are fibroadenomas or cysts.
- 10% fibroadenomas are multiple.
- It is benign breast disease with epithelial elements and fibrous tissue stroma.

The incidence decreases with age and specially after menopause.

It may calcify and be diagnosed easily on mammography. It is very mobile but with age, the mobility decreases (Breast mouse).

It is commonly present in the upper and outer quadrant of the breast. Its size varies from 1 cm to 15 cm range.

The lesion is usually firm or hard with well demarcated borders. It is extremely mobile and slips from the examining hands easily. It is also called “Breast mouse”. Two histological variants are described depending upon the predominance of the tissue.

INTER CANALICULAR FIBROADENOMA

It is the most common type. Fibrous tissue predominates and projects into the lumen of the ducts distorting their shape. It may be occasionally bilateral.

Cystic and sarcomatous changes sometimes supervene.

PERICANALICULAR FIBROADENOMA

It is small well encapsulated tumor. Both the fibrous and epithelial tissue have overgrown in a way that these resemble normal breast lobule.

Following investigations help in the confirmation of the diagnosis;

- Mammography.
- FNAC.
- Trucut needle biopsy.
- Excision biopsy.

FNAC or trucut needle or excision biopsy confirms the diagnosis[2].

TREATMENT

WOMEN BELOW 25 YEARS OF AGE

Only symptomatic treatment may be required.

Reassurance and regular follow up clinical examination is enough.

Surgery may be offered for psychological or cosmetic reasons because of presence of the tumor.

and shiny skin on affected side.

Bigger fibroadenomas sometimes becomes lobulated and leaf like and is called Phyllodes tumor which may be benign or malignant.

The giant fibroadenoma can be benign, locally invasive and rarely a malignant tumor.

Malignant tumors are called Phyllodes tumors (previous names were cystosarcoma phyllodes or phyllodes sarcoma).

TREATMENT

Surgical removal through an appropriately cosmetic incision is carried out.

The discrepancy in size following surgical removal settles in a year or two.

PHYLLODES TUMORS

Previously named as cystosarcoma phyllodes or phyllodes sarcoma, these tumors show a wide spectrum of activity from completely benign to locally invasive and occasionally metastatic tumor.

Histopathologically it harbors a sharp demarcation from surrounding tissue. Connective tissue composes bulk of mass. The cystic component is due to areas of infraction, degeneration and necrosis. These alterations give the breast its classic leaflike (Phyllodes) appearances. The contour may assume a tear drop configuration[7,8].

Stroma shows hypercellularity, much atypia and numerous mitoses.

CLINICAL FEATURES

Clinically they present with features similar to fibroadenoma but progress rapidly to a large size, sometimes with ulceration of skin or involvement of axillary lymph nodes.

Metastasis occur in less than 5% of the tumors.

TREATMENT

Simple enucleation is performed before the age of 20 years.

Elderly patients require wide local excision with one cm margin, 25% tumors recur[8], these need to be excised with wide margins.

Very large tumors or those with aggressive histology merit simple mastectomy and reconstruction.

NON PROLIFERATIVE LESIONS
BREAST CYSTS

Upto 7% women develop a cyst once in their life. Two distinct populations of cysts appear to exist, simple and apocrine. These are defined by their microscopic appearance, biochemical

Ultrasound examination of breast and aspiration confirms diagnosis;

TREATMENT

i. Aspiration.
Ii. Surgical Excision.

- Aspiration which can be repeated for one more occasion.
- If it does not settle or aspirate is blood stained, then surgical excision is performed.
- Patients with recurrent apocrine cysts may benefit from continued mammographic surveillance and no surgical intervention.

GALACTOCELE

It presents as a cyst in women who have recently stopped breast feeding. It is probably simply cyst filled with milk.

Aspiration is diagnostic as well as therapeutic.

FAT NECROSIS

Fat necrosis is a frequent cause of diagnostic difficulty in women. A history of trauma is easily provided. The lump may be hard and confused with carcinoma. Even mammographic findings are similar to those of cancer.

FNAC is diagnostic.

Lump may have to be excised if the doubt exists[31].

SCLEROSING ADENOSIS

It is uncommon cause of breast lump. It is charact-erized by proliferation of terminal duct lobules, myoepithelial cells with increased number of acini and fibrous stromal change. It presents as a smooth but mobile mass in 30-50 years age group. It may have a stellate appearance and may calcify thus it may mimic carcinoma both clinically and radiologically. The increased cellularity can be confused with carcinoma histologically. It may be painful. FNAC and trucut biopsy is diagnostic.

Lump may necessitate excision because of pain or patient's fear[8,11,25].

LIPOMA / ADENOLIPOMA

Lipomas present as a soft smooth, mobile lumps quite frequently. These may be having a glandular component-adenolipoma. These are best excised if there is any doubt.

DISORDERS OF NIPPLE AEROLA COMPLEX
NIPPLE DISCHARGE DUCT ECTASIA & PERI-DUCTAL MASTITIS

Duct ectasia and peri-ductal mastitis represent a spectrum of inflammatory processes where the sub-areolar ectatic, enlarged, ducts are surrounded by a mild inflammatory infiltrate[31].

PATHOGENESIS

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CLINICAL FEATURES

Creamy discharge from multiple, bilateral ducts is a feature of duct ectasia. Periductal mastitis may present as a mass or an abscess. Repeated inflammation results in retracted slit shaped nipple in contrast to retraction seen with an underlying cancer when it is circumferential.

TREATMENT

Antibiotics are to be given for periductal mastitis. Abscess necessitates incision and drainage. Sometimes core excision of major duct system has to be done if it is referactory to treatment with antibiotics or if the discharge persists[32].

NIPPLE INVERSION & RETRACTION

Inversion describes a congenital failure of eversion during development and retraction is usually due to duct ectasia or carcinoma.

TREATMENT

For inversion, surgery is usually unnecessary, it resolves mostly during pregnancy and lactation. Cosmetic surgery is performed for inversion or retraction due to duct ectasia but it has drawback of dividing ducts[32].

BREAST ABSCESS

It is the collection of pus in the breast. Commonly it is seen in the lactating breast. The abscess remains contained in the lobes of breast localized by the fibrous septa. The induration lasts longer.

The abscess typically occurs within first few weeks of lactation and breast feeding.

It is most often staphylococcal in nature. Bacterial invasion of the breast tissue leads to development of acute mastitis. The localization of abscess occurs easily. Multi-locular abscess is typically staph-ylococcal.

The bacterial access is through the lactiferous ducts when there is inspissation of secretions in the ducts or cracks and fissures in the nipple during early periods of nursing. These changes follow dermatitis of nipple.

The inflammatory process leads to cellulitis with localized subcutaneous, sub-areolar, interlobular, peri-ductal and retromammary collection of pus.

Commonly the breast abscess is unilateral, it may be unicentric or multi centric collection. It may be a single abscess or multiple abscesses may be present.

Streptococcal infection tends to cause diffuse spreading infection and involves larger areas. It is localized at a later stage.

The abscess presents with painful

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OBJECTIVES OF MANAGEMENT

Objectives of management are;

1. Assessment of general condition of the patient.
2. Confirmation of diagnosis.
3. Immediate treatment for relief of symptoms.
4. Definitive treatment of the cause.

The patient is investigated thoroughly for general assessment and confirmation of diagnosis. Complete urine examination and blood examination is performed and ultrasound of the breast is performed.

Fluctuation becomes elicitable at a late stage. The skin necrosis occurs by the time fluctuation is positive. The breast abscess is drained at an early period when it is still in the induration stage.

Surgical drainage of abscess with complete breakage of all loculi is the adequate treatment of breast abscess. Thorough Debridement of the abscess is required for good cosmetic results and prevention of recurrent abscess.

Discontinuation of the lactation by using anti prolactin drugs (Bromocriptine) helps to resolve the inflammatory process by regression of lactation.

Breast suction with the help of breast suction pump helps to get rid of the thick milk secretion but stimulates further lactation and may not be always helpful in resolution of inflammatory process.

Breast abscess may resolve or be cured with adequate treatment. It may progress to form chronic or recurrent abscess with improper or inadequate treatment.
Chronic or recurrent abscess is investigated for acid fast bacilli, fungi, aerobic and anaerobic bacteria.

Thorough debridement and use of appropriate antibiotics for longer period may be used.

Simple mastectomy may be required in worse cases to treat and avoid the worse chronic infection.

IMMEDIATE TREATMENT

Analgesia can be given both by mouth or parent-erally to relieve the pain.
Focal heat compresses are used.
Parenteral or oral antibiotics against gram positive cocci are used in adequate doses.
Ultrasound guided aspiration of pus collection is performed.
The conservative treatment is continued for 2-3 days.
If the symptomatic relief is obtained, the treatment may be continued for few days till complete relief.

Incomplete drainage leads to healing with fibrosis and scarring. It may occasionally be mistaken as malignancy. It should be completely drained by breaking all the loculi to

mass. Spontaneous resolution is common but these may progress to an abscess. Systemic features are less marked.

TREATMENT

Treatment is aspiration and obtaining pus for culture & sensitivity. A combination of flucloxacillin and metronidazole is recommended. Repeated aspirations may be helpful. Occasionally drainage is required and must be done through smallest possible incision.

Definitive treatment is major duct excision and nipple eversion when acute inflammation has settled. It should be performed under proper antibiotic cover.

MASTITIS NEONATORUM

Breast abscesses can rarely occur in neonates due to infection of milk induced by transplacental passage of maternal hormones.

Treatment is antibiotics.

Occasionally, surgical drainage is necessary and may lead to distortion of breast contour in later life.

MAMMARY FISTULA

It may follow spontaneous or surgical discharge of an abscess and is found at areolar margin. Characteristically the breast demonstrates multiple incisions for drainage of previous abscesses, distortion, nipple retraction, and a fistula at areolar margins. Basic cause is duct ectasia/periductal mastitis.

Treatment is fistulectomy and excision of offending duct. Occasionally major duct excision is necessary[32].

MISCELLANEOUS BENIGN BREAST CONDITIONS
CRACKED NIPPLE

It occurs during lactation and is the forerunner of acute bacterial mastitis. Breast should be rested for 24-48 hours and evacuated with breast pump. Then feeding may be resumed.

PAPILLOMA OF THE NIPPLE

It has features similar to other cutaneous papillomas and should be excised with a tiny disc of skin.

SEBACEOUS CYST

It results from blockage of duct of gland of Montgomery situated in areola. It may be excised for cosmetic indications.

CHANCRE OF NIPPLE

It is very rarely seen. It results from infection from a syphilitic buccal ulcer of the partner.

Treatment is as for syphilis.

or infection.

The veins appear as thrombosed subcutaneous cords attached to skin. A groove appear alongside the cord on lifting the skin. It is to be differentiated from lymphatic inflammation from occult carcinoma breast.

TREATMENT

Restriction of the arm movements is required. It resolves spontaneously within a few months in any case.

HAEMATOMA

Presents with a lump and history of trauma. Only aspiration or incision is diagnostic as well as therapeutic.

CONGENITAL ABNORMALITIES OF THE BREAST
AMAZIA

Congenital absence of the nipple may be unilateral or bilateral. Occasionally it is accompanied by missing sternal portion of pectoralis major (Poland's synd). It is more common in males.

POLYMAZIA

Accessory breasts have been recorded in axilla (most common), groin, buttock and thigh. These function during lactation only.

DIFFUSE HYPERTROPHY

It occurs occasionally in otherwise healthy girls at puberty and less often during first pregnancy. Breasts attain abnormally large size.
The enlargement condition is mostly bilateral. Increased sensitivity to estrogen has been suggested as a cause.

Some success has been reported with treatment with antiestrogens. Otherwise, reduction mammoplasty is the treatment of choice.

GYNAECOMASTIA[26,27,28,29]

Gynaecomastia is the abnormal growth of breast tissue in males. It is a benign and often reversible condition which affects 3% of the male population once in a lifetime.

Mostly it occurs in teenage boys (pubertal gynaecomastia) and elderly man (senescent gynaecomastia). Together these account for 50% of patients.

AETIOLOGY

Basically there is disturbance in the estrogen androgen ratio leading to relative hyperestro-genism. It may be;

i. PHYSIOLOGICAL

- Neonatal.
- Puberty.
- Old age.

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Lymphomas
Gastric carcinoma
Renal cell carcinoma

- Systemic Diseases
  Chronic liver disease
  Renal failure on dialysis
  Thyrotoxicosis
  Starvation/Refeeding

- Hypogonadal States
  Klinefelter's syndrome
  Secondary testicular failure

- Drugs
  Oestrogens
  Androgens
  Cyproterone acetate
  Cardiac glycosides e.g. Digoxin

H2 Blockers and PPI's such as cimetidine, ranitidine and omeprazole

Diuretics e.g.spironolactone.
Tricyclic antidepressants.

The cause of breast enlargement in hyper androgenic states is peripheral conversion of androgens to estrogens by the enzyme called aromatase leading to relative hyperestrogenism.

Drugs and metabolic diseases interfere with metabolism of estrogens.

TREATMENT

If unilateral and found in elderly FNAC must be done to rule out carcinoma of the male breast.
Reassurance of the patient that this is purely a benign disease which is usually reversible will suffice in most of the cases.

If persistent and leading to social embarrassment or causing pain, then surgery has to be performed. Cessation of drugs should lead to spontaneous resolution.

The surgical treatment is subcutaneous mastectomy using a circumareolar incision. Sub-mammary or a Thomas-Gallard incision is employed for larger breasts .

Liposuction has no role in the treatment of gynaeco-mastia as breast tissue is not fat alone.

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Fig-11.1 Breast abscess with necrosis of over lying skin
Courtesy Sajid Shiekh, FCPS

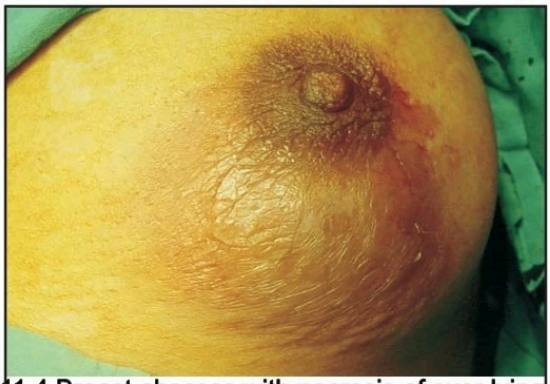


Fig-11.4 Breast abscess with necrosis of over lying skin
Courtesy Sajid Shiekh, FCPS

Fig-11.2 Left breast abscess (Huge size)

Fig-11.5 Fibroadenoma breast (per operative appearance)

Fig-11.3 Bilateral hypertrophic breasts

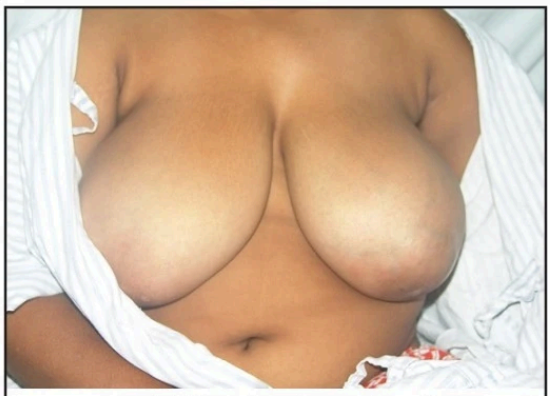


Fig-11.6 Bilateral hypertrophic breasts

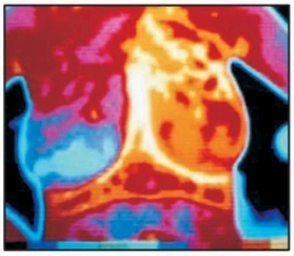
Chapter-12

Non Invasive Carcinoma of Breast

Ductal Carcinoma in Situ (DCIS)
Lobular Caracinoma in Situ (LCIS)
Paget's Disease of Nipple

Objectives

- To detect the carcinoma breast at a very early stage (non invasive stage).
- To confirm the diagnosis.
- To plan satisfactory and adequate management.
- To establish an adequate follow up plan.



NON INVASIVE CARCINOMA OF BREAST

Shuja Tahir, FRCS, FCPS

Carcinoma breast is a dreadful condition. The women feel severely depressed even at the thought of suffering from this problem.

Its understanding is improving with the time. The methods to detect the condition at earliest have been developed and are being further improved.

New methods are being explored. The patients at risk are identified and managed to avoid invasive disease.

Relationship between benign and malignant disease based on the consensus statement of the American college of Pathologist is as follow[1,5];

NO INCREASED RISK

Sclerosing adenosis.
Aprocrine change.
Duct ectasia.
Mild hyperplasia.
Fibro adenoma.
Apocrine metaplasia.

SLIGHT INCREASED RISK(1.5-2 TIMES)

Moderate or florid hyperplasia
Papilloma with fibro vascular core.

MODERATE INCREASED RISK (4-5 TIMES)

Atypical ductal hyperplasia.
Atypical lobular hyperplasia.

HIGH RISK (8-10 TIMES)

Ductal carcinoma in situ (DCIS)
Lobular carcinoma in Situ (LCIS)

NON INVASIVE CARCINOMA OF BREAST

It includes (Grade I or Type I Non Metastasizing).

- Intra ductal carcinoma of breast, Ductal caricnoma in situ of breast (DICS).
- Intra ductal carcinoma with Paget's disease.
- Lobular carcinoma in situ (LCIS).

INTRA DUCTAL CARCINOMA
DUCTAL CARCINOMA IN SITU (DCIS)[2]

includes heterogenous group of lesions with diverse clinical presentations, histological features and biological potential.

Ductal carcinoma in situ is the transformation of ductal epithelial cells into malignant cells that remain in the anatomical position and have not yet broken through the basement membrane.

It is a local disease which has not changed into a systemic or invasive disease therefore, it is called carcinoma in situ.

The number of patients having DCIS have grown 10 times from (2% -20%) during last twenty years. It represents 15-20% of breast carcinomas detected by mammography. It is seen in 95% of cases of DCIS. Nearly 60% of DCIS cases are solely discovered by mammography[2,7].

Intra ductal carcinoma is much more common than lobular carcinoma in situ. It is seen in 5% of all symptomatic breast cancers.

It is usually diagnosed mammographically by detection of micro calcifications. A mass greater than 1cm at mammography represents malignancy in approx 25% of cases (most of these are invasive lesion).

Calcium deposits in DCIS are dystrophic calcifications secondary to necrotic tumor cells. The number of clusters of microcalcification, branching or linear calcification are likely to be associated with malignancy[2,7].

Its presentations are variable. It presents with a mass in breast or nipple discharge. The palpable lesions of DCIS are multicentric. These show occult invasion and overall poor prognosis.

It may produce a mass or present as paget's disease of nipple or as a discharge from nipple.

Non Invasive carcinoma of breast is the initial stage of breast malignancy. The special feature is non invasion of basement membrane with tumor.

These cancers don't have the ability to metastasize at this stage as these are confined to the cells.

It begins as atypical proliferation of ductal epithelium that eventually completely fills and plugs the ducts with neoplastic cells. There is marked dilatation of ducts with solidification. All these changes may create some change in consistency of breast substance. The ducts are filled with necrotic and cheesy material which can be extruded upon slight pressure. It is also called comedo carcinoma.

Histopathological findings are dilated ducts filled with neoplastic epithelial cells. Some glandular or papillary

HIGH GRADE DCIS

It is the easiest to identify. The tumor cells have pleomorphic nuclei, irregular nuclear contours, prominent nucleoli and frequent mitosis. Multiple growth pattern may be seen often with central necrosis and calcification.

LOW GRADE DCIS

It shows a uniform group of cells in cribriform or micropapillary pattern. There is lack of necrosis or cytologic Atypia.

INTERMEDIATTE GRADE DCIS

It shows proliferating cells with mild to moderate Atypia and variable growth patterns such as cribriform, micropapillary or solid lesion with prese-nce of central necrosis.

The lesion advances and leads to invasion of basement membrane and it changes to infiltrating ductal carcinoma (Invasive carcinoma).

COMEDO VARIETY

DCIS may not present with clinically palpable mass. Some times there is palpable cord like thickening. Cheesy material of necrotic tumor extrudes out on cutting and pressing the cord. It is then called comedo carcinoma. It may be of large size and may have high rate of recurrence. 40% of comedo type intra ductal carcinomas are of high grade. Invasion may occur some time later.

CRIBRIFORM VARIETY

Histologically the ducts may be more or less filled with masses of anaplastic tumor cells creating small glandular spaces. It is called cribriform type. It carries better prognosis than comedo variety.

MICROPAPILLARY VARIETY

Some lesions present with ducts filled with solid masses of cells and sometimes with central areas of necrosis which may calcify showing as micro calcification on mammography. Sometimes cells grow in papillary formations. It is called micro-papillary variety. It has better prognosis than comedo variety.

PAGET'S DISEASE OF NIPPLE

Rarely anaplastic cancer cells extend into the epidermis of nipple and areola to produce Paget's disease of nipple. DCIS is the most frequently detected abnormality and appears as a cluster of pleomorphic calcification.

It runs 30-50% risk of developing into invasive carcinoma over 15 years.

BIOLOGIC MARKERS OF DICS[1]

Biologic markers help in the diagnosis of intraductal carcinoma. These are as follows;

- There is increase in microvessel density around the ducts involved in DCIS.

All these markers indicate poor prognosis after the development of invasive carcinoma.

CLINICAL FEATURES OF INTRADUCTAL CARCINOMA

The intra ductal carcinoma may present with the following features;

- Lump.
- Nipple discharge.
- Paget's disease of breast (It is an extension of intraductal carcinoma to nipple areola complex involving its epidermis).
- Asymptomatic patient with mammographic findings.

MAMMOGRAPHIC FINDINGS FOR DCIS

- 75% present with calcification (linear, branching, granular or heterogenous).
- 10% present as soft tissue mass.(well circumscribed mass, architectural distortion and developing density)
- 12% present as combination of the above.

LOBULAR CARCINOMA IN SITU (LCIS)

It is usually diagnosed incidently while reviewing biopsy tissue for some other lesions. It is more of a marker for development of cancer in future. It may lead to development of both ductal or lobular carcinoma.

It is a distinct type arising from terminal ducts and ductules.

These structures get distended with necrotic anaplastic cells in the center of ductule.

There are fibrocystic changes mixed with intra ductal carcinoma even invasive carcinoma.

The carcinomatous lesion is usually multi focal and bilateral. One third of LCIS change into invasive carcinoma over a period in the same or opposite breast. Many change to ductal carcinomas. The monitoring or prophylactic treatment of opposite breast is also performed.

PAGET'S DISEASE OF BREAST

It is a breast lesion which present as a chronic eczematoid eruption of nipple areola complex. It was first described by Sir James Paget in 1874. It is seen in approximately 02% of patients.

The specific demonstration of carcinoembryonic Antigen (CEA) within the paget cell facilitates in diagnosis and its differentiation from malignant melanoma lesions. The origin of paget cells is not clear. It may be formed due

Paget's disease of breast is a type of ductal carcinoma which extends from the ducts to involve the skin of nipple and areola. The malignant invasion of the nipple presents as eczematous change of unilateral nipple and areola. It may present as an encrusted and scaby tumor present at nipple and areola.

The involved skin is ulcerated, fissured and oozing. It may have surrounding area of inflammatory hyperaemia and edema. Advanced cases show total ulceration or even loss of nipple and areola. There may be superimposed infection and suppurative necrosis. Its symptoms include tenderness, itching, burning and intermittent nipple discharge.

The underlying mass or lump in rarely palpable.

Histologically it is an extension of intra ductal carcinoma or even infiltrating ductal carcinoma.

It occurs in old age group of patients very rarely it may even present as early as 20 years of age.

The epidermis is involved by the malignant cells and these are called. "Paget's cells". Their origin and nature is unknown. The intraductal lesion is often multifocal and ducts throughout breast may be dilated due to obstruction of central collecting ducts at the ampula. Paget's cells are large, anaplastic and hyper-chromatic ovoid cells surrounded by a clear zone or halo. These have pale cytoplasm. It is possibly due to ballooning degeneration. The anaplastic tumor cells lie singly or in clusters within the epidermis.

30-40% of these patients have metastasis at the time of surgery and prognosis is less favorable than simple intra ductal carcinoma which is diagnosed at earlier stage.

Treatment Outcomes in DCIS: French Experience			
Local Therapy	**Mastectomy**	**Lumpectomy**	**Lumpectomy+XRT**
No. of Cases	306	403	842
% of local-regional recurrence	1.6%	26%	12.7%
No. of in situ recurrence	0	52	38
No. of invasive recurrence	5	53	65
No. of axillary recurrence	1	9	14
No. of metastatic recurrences	2	5	11
% of metastatic recurrences	0.6%	1.2%	1.3%

The objectives of treatment of non invasive carcinoma breast are[4,8];

- To prevent the development of invasive and life threatening breast carcinoma.
- To offer minimum but sufficiently curative treatment.
- To preserve breast if possible.

Following options are available;

Lumpectomy.
Lumpectomy with radiation.
Lumpectomy, radiation and tamoxifen.
Radiation.
Radiation with tamoxifen.
Mastectomy.
Aromatase inhibitors and tamoxifen.

LUMPECTOMY (WIDE EXCISION OF THE LUMP)

It is removal of the diseased tissue with some macroscopically healthy tissue around. The local recurrence and its development to invasive carcinoma breast is seen in about 18% of the patients after this treatment. It is not a good method of treatment even though it conserves the breast.

LUMPECTOMY AND RADIOTHERAPY

It is a good alternate as it gets rid of the disease process and conserves the breast. It also minimizes the local recurrence and development of invasive carcinoma. The overall survival is similar to that of mastectomy patients.

It seems to be the most effective method of present day treatment. It provides good, cosmetic results and may prevent the psychological trauma. It has some risk of progress of disease process.

MASTECTOMY

Mastectomy provides nearly 100% cure from this entity. The local recurrence rate is approximately 0.75% and mortality rate of 1.7% has been demonstrated. Ipsilateral mastectomy is adequate because overall incidence of occult disease (10-15%) is equivalent to the invasive carcinoma breast.

It is probably the best treatment but loss of breast may not be acceptable to all women without psychological effects.

MASTECTOMY WITH BREAST RECONSTRUCTION

It is an improvement on the mastectomy alone. Reconstruction of breast is a growing speciality which may incorporate implantation of prosthesis of various materials or reconstruction by using myo-cutaneous flap.

Letrozole (Aromatase inhibitor) therapy improves disease free survival in patients with early-stage breast cancer in patients after completion of tamoxifen therapy[3].

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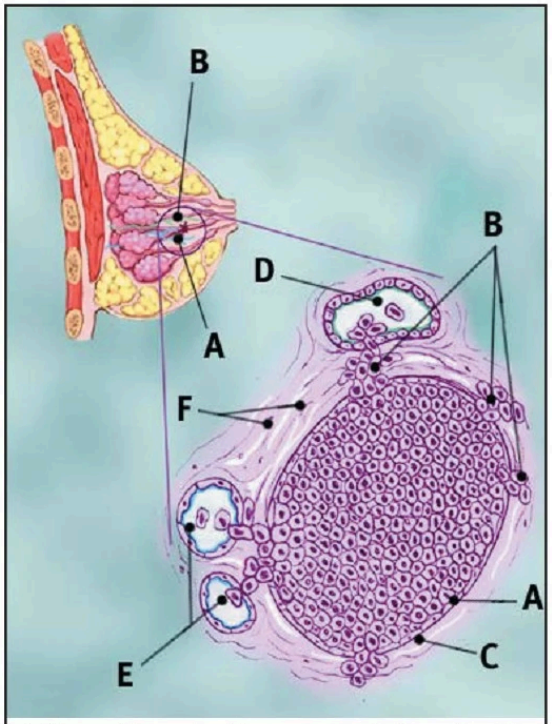

Fig-12.1 Normal breast with cancer cells invading the lymph channels and blood vessels.

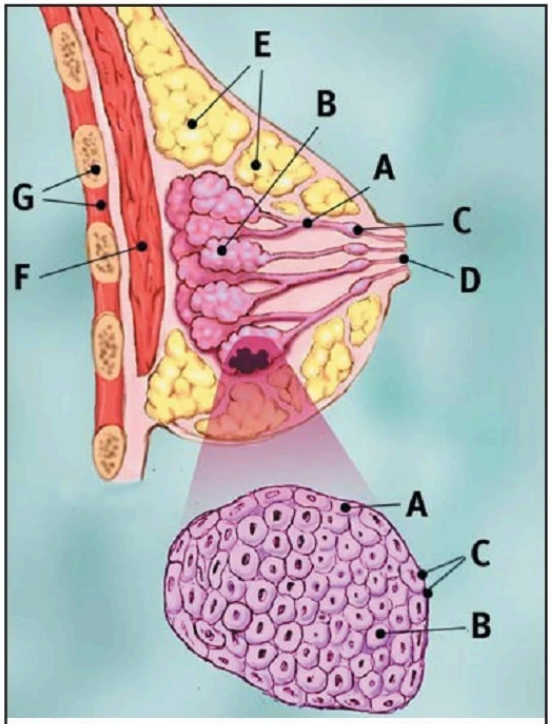

Fig-12.3 Lobular Carcinoma in situ (LCIS)

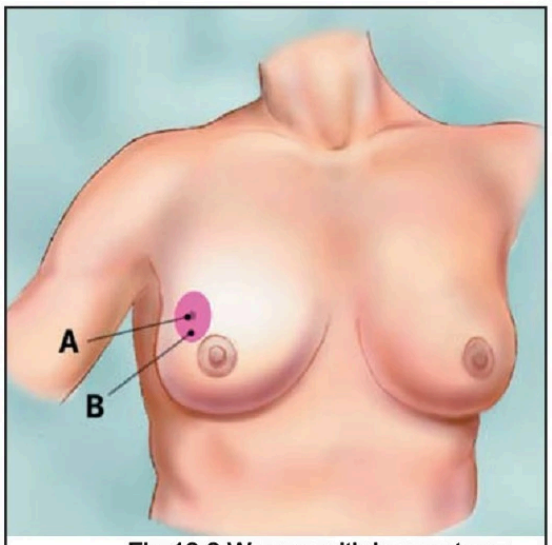

Fig-12.2 Woman with lumpectomy.
(A) Tumor
(B) Tissue removed at lumpectomy

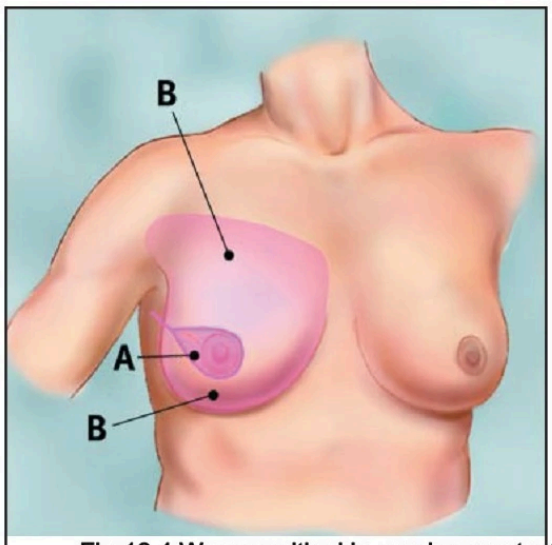

Fig-12.4 Woman with skin-sparing mastectomy
(A) Pink line indicates keyhole like incision
(B) Tissue removed at mastectomy

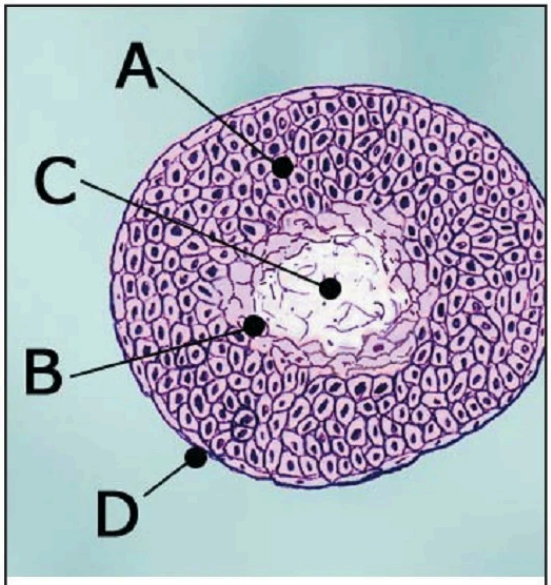

Fig-12.5 Non-Invasive Cell Growth Subtypes Comedo. (A) Living cancer cells. (B) Dying cancer cells. (C) Cell debris (necrosis). (D) Basement membrane.

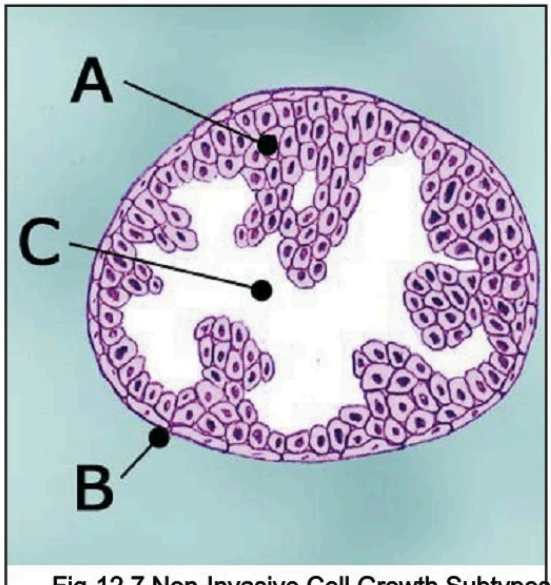

Fig-12.7 Non-Invasive Cell Growth Subtypes Papillary
(A) Cancer cells.
(B) Basement membrane.
(C) Lumen (center of duct).

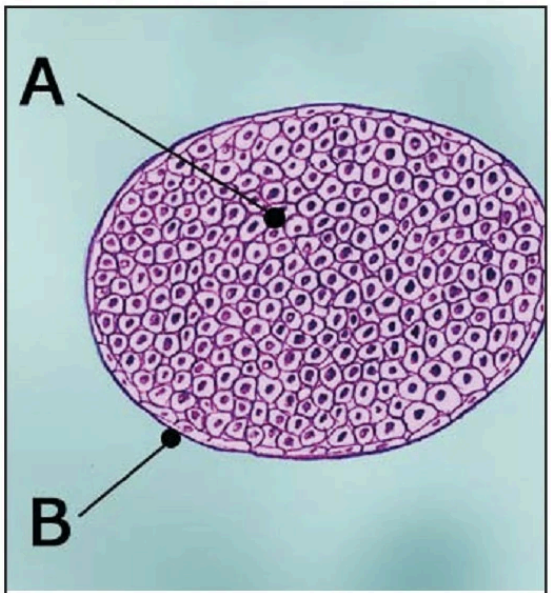

Fig-12.6 Non-Invasive Cell Growth Subtypes Solid
(A) Cancer cell. (B) Basement membrane.

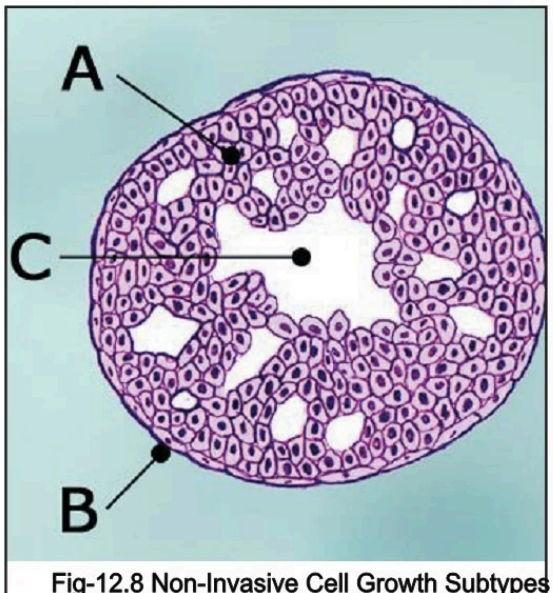

Fig-12.8 Non-Invasive Cell Growth Subtypes Cribiform
(A) Cancer cells.
(B) Basement membrane.
(C) Lumen (center of duct).

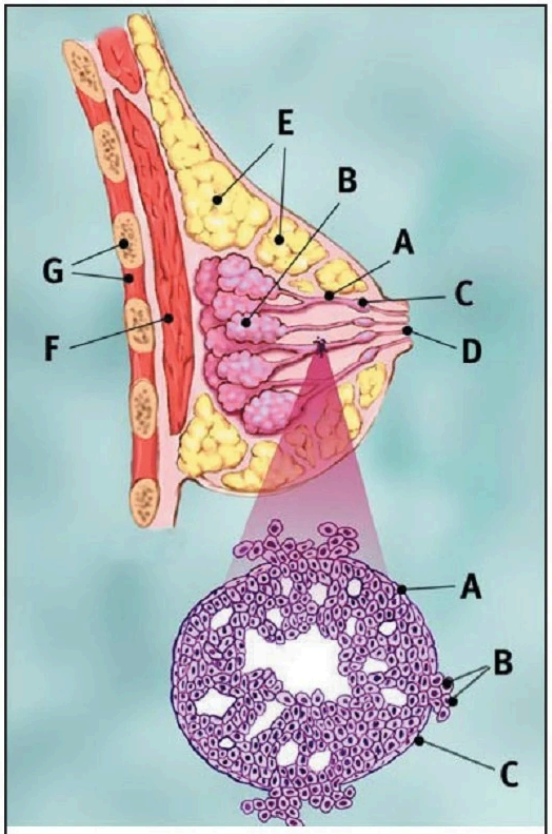

Fig-12.9 Invasive Ductal Carcinoma (IDC)

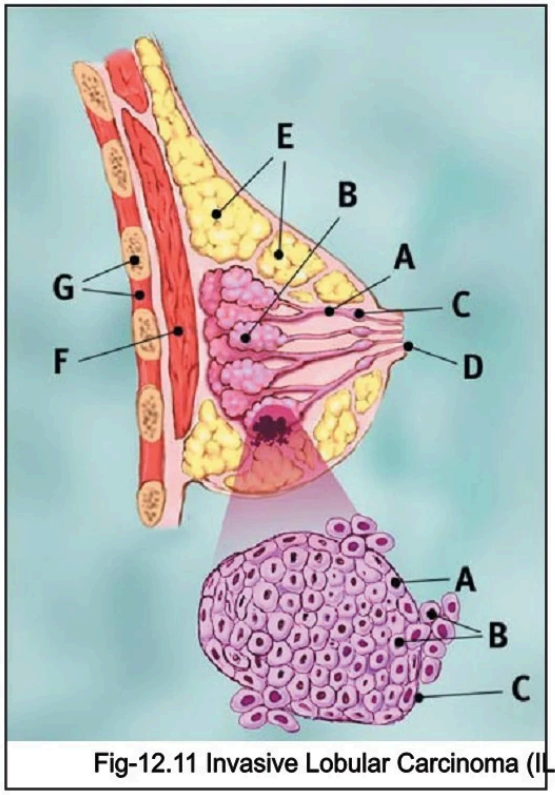

Fig-12.11 Invasive Lobular Carcinoma (ILC)

Fig-12.10 Paget's disease of nipple (advanced stage)

Fig-12.12 Paget's disease of nipple
Courtesy Sajid Shiekh, FCPS

Chapter-13

Invasive Carcinoma of Breast

Minimum Carcinoma Breast
Early Carcinoma Breast
Invasive Carcinoma Breast

Objectives

- To diagnose the lesion correctly.
- To assess the extent of malignancy locally (T-staging).
- To assess the extent of malignancy regionally (N-staging).
- To assess the extent of malignancy systemically (M-staging).
- To plan best possible management options.
- To counsel the patient effectively.

INVASIVE CARCINOMA OF BREAST

Shuja Tahir, FRCS, FCPS

Invasive carcinoma of the breast is the malignant tumor of the breast which has already crossed the basement membrane. It is minimally invasive when it is less than 1 cm in its greatest diameter and is node negative (Early Invasive Carcinoma). It is maximally invasive and advanced or metastatic carcinoma when it is bigger than 10 cm in its greatest diameter.

Carcinoma of the breast is the most common cancer in the women of the 35-50 years age group in western society. In our country exact records are not available. Occasionally males can also suffer from this dreadful disease.

Understanding of the fact that breast cancer is not a local problem but systemic disease has changed the methods of treatment of patients with breast carcinoma.

INCIDENCE

It is the most common malignancy of women at present.

Breast cancer is number one killer of women due to any malignancy.

Seven out of every hundred women are likely to suffer from carcinoma of the breast.

It is 2-3 times more common in women with family history of carcinoma of breast.

Females of a family with mutated genes have 80% risk of developing breast cancer by the age of 80 years.

Male to female ratio is 1 : 100.

It accounts for 27-32% of all female malignancies.

It is more common in single women than in married women.

It is more common in nulli-parous women.

It is rare before 25 years of age.

It is more common in women with early menarche (Before 11 years of age) and late menopause (after 55 years of age).

It is more common in jews.

It is common in upper and outer quadrant.

Low fat diet is associated with lower incidence.

It is more common in obese women than in slimers.

Second carcinoma breast occurs (second primary tumor SPT) in 4% of the patients of carcinoma breast.

90% carcinomas of breast occur in the ductal epithelium.

10% carcinoma occurs in lobules of the breast.

5-10% of all breast cancers result from autosomal dominant inheritance of a mutated gene[1].

The incidence is rising. This rise may be due to better and early diagnosis.

The incidence of breast cancer is six times higher in U.S.A., Canada and Europe than in Asia and Africa.

Japan has low incidence.

Carcinoma breast causes nearly 10,000 to 30,000 deaths every year in U.S.A only.

ETIOLOGY

The exact cause of breast cancer is still not known. Its etiology is multi-factorial.

There are many risk factors which are associated with the development of carcinoma of breast;

SEX
Females are 100 time more at risk for the development of breast carcinoma. Hormonal or genetic factors common in females may be responsible for its occurrence.

AGE
The risk of breast carcinoma in 20-40 years old patient is 0.5% but it is 5% in patients of 50-70 years age group (10 times more). This is the reason for patients (Above 50 years) presenting with carcinoma breast at a higher age.

The incidence of carcinoma breast increases with increase in age particularly in women above 50 years of age.

HORMONAL EFFECTS

Hormonal influence over a prolonged period may be responsible for greater number of cycles of stimulation and involution breast tissue. The breast tissue undergoes proliferation and involution under the prolonged hormonal influence.

Greater the number of cycles, greater the risk of malignancy.

The period between menarche and menopause is significant risk. Longer period due to early menarche and late

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insignificant risk for carcinoma breast.

Bilateral oophorectomy in pre-menopausal women greatly reduces the risk of carcinoma breast.

PREVIOUS BREAST CARCINOMA

The chances of having cancer breast in patients who have been successfully treated, are more than normal population. It may be part of multifocal tumor or an entirely new primary carcinoma (second primary tumor: SPT). Its risk is more in younger females especially if the first breast carcinoma is diagnosed before the 40 years of age.

Patients with single breast cancer are at risk of having second primary tumor (SPT). Efforts should be made for early detection of cancer breast with the help of triple assessment (clinical examination, mammography and FNAC).

FAMILY HISTORY

It is a well established risk factor for the development of carcinoma breast.

Familial breast cancer is the one which is seen in first degree relatives (mother, sister or daughter) and second or higher degree relatives (grand mother, aunt, cousin).

History of breast, ovarian, prostate and colonic carcinoma in the family members predisposes to increased incidence of carcinoma breast.

PARITY

Single or nulli-parous married ladies are at a higher risk of carcinoma breast. The protective effect of full term pregnancy and parity is seen only in younger females (20-30 years age).

Independent protective effect of breast feeding has not been confirmed yet.

HEREDITARY

Hereditary breast cancer is a breast cancer in the patients in which it is related to autosomal dominant inheritance of a mutated gene[2].

All cancers are genetic at the cellular level in a way that these result from accumulation of genetic abnormalities leading to genome instability and loss of normal growth regulation.

There is accumulation of three to six mutations for the development of sporadic solid tumor. 5%-10% of all breast cancers are hereditary.

PATHOLOGY

The carcinoma of the breast arises from duct epithelium; Terminal duct lobular unit (Tdlu).

The histological picture is variable. Some are less malignant and retain

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feature of histology in carcinoma breast is usually an infinite variation in the pattern of the cancer cells from the atrophic schirrous with much fibrous tissue to the most cellular with little or no fibrous tissue.

While the lump may be obviously schirrous, deposits in the lymph gland may be highly cellular.

It is possible however to distinguish between those arising in the nipple (Paget's disease) and those arising in the ducts, which are frequently papilliferous in form.

Those arising in the breast tissue itself are composed mainly of spheroidal cells with varying degrees of fibrous tissue response.

A distinct type is called colloid carcinoma where all the neoplastic cells are distended with colloid material. This leads to form a large growth but is not as highly malignant as might be expected.

Invasive ductal carcinoma of breast is the most common type of cancer breast 70-80% of carcinomas of breast are ductal in origin.

The ductal carcinomas produce a desmoplastic response and replace normal breast fat forming a hard palpable mass.

The microscopic appearance is heterogeneous ranging from tumors with well developed tubule formation and low grade nuclei to anaplastic tumor.

The tumor margins are irregular but occasionally may be circumscribed. Lympho vascular invasion may be obvious. Dimpling of skin may be seen in advanced carcinoma.

Retraction of nipple and tumor invasion into chest wall may be seen histologically. 66% of carcinoma of breast may show hormone receptor positivity and nearly 33% may be HER-2 neμ positive.

INFLAMMATORY CARCINOMA

It may present as an enlarged erythematous breast without discrete palpable mass. The underlying malignancy is diffuse in nature. The blockage of dermal and lymphatic spaces by malignancy result in such appearance.

Inflammation as such is either minimal or not present at all. These tumors are usually metastasized and have very poor prognosis.

INVASIVE LOBULAR CARCINOMA

These tumors are less than 20% of all breast tumors. 66% of these cases are associated with LCIS. The cellular invasion is present into the stroma. It is arranged in strands or chains.

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in form of large anaplastic cell sheets and have well circumscribed borders. Clinically these resemble fibro adenomas. There is almost always pronounced lymphoplasmocytic infiltration. These are commonly seen in women with BRCA1 mutations.

COLLOID (MUCINOUS) CARCINOMA

It is also a rare type of tumor. Large quantities of extracellular mucin is seen in the stroma. These tumors present as circumscribed masses and look similar to fibro adenomas. The tumor is soft and gelatinous. Many of these tumors may be hormone receptor positive.

TUBULAR CARCINOMA

These are 10% of invasive carcinoma of less than 1 cm size found by mammography. These present as irregular densities on mammography.

Microscopically these present as well defined tubules with low grade nuclei. Lymphatic spread is rare and prognosis is excellent. These are usually hormone receptor positive.

Carcinoma of the breast is a disease which dissemi-nates early but recurs late. Two main factors affect the outcome of treatment;

The extent of the disease (staging).
The nature of carcinoma breast (grading).

GRADING OF THE TUMOR

It means the nature (grading) of the tumor (whether the tumor is well differentiated or not). Nature of the growth affects prognosis of the disease.

Microscopic variations of histological picture are classified as different grades of tumor depending upon the growth pattern. Following features are taken into account while the tumor of the breast are graded;

Tubule formation.
Irregularity in size, shape and staining of nuclei (pleomorphism).
Number of mitoses.

Tumors with glandular or tubular histological pattern which have marked lymphocytic infiltration or elastosis and those with high concentration of oestrogen receptor proteins have relatively good prognosis.

Tumors provoking good host reaction (regional lymph node hyperplasia) have good prognosis as well. Histological types (grades) of carcinoma breast are following;

GRADE 1
TYPE 1 (NON METASTASIZING)

It includes following conditions;

Ductal carcinoma in situ (Intra ductal carcinoma) (DCIS).
In situ lobular carcinoma (LCIS).

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Pure extracellular mucinous or colloid carcinoma.
Medullary cancer with lymphocytic infiltration.
Well differentiated tubular adenocarcinoma.
Adenoid cystic carcinoma.

GRADE III
TYPE 3 (MODERATELY METASTASIZING)

It includes ;

Schirrous carcinoma.
Ductal carcinoma with stromal involvement.

GRADE IV
TYPE 4 (HIGHLY METASTASIZING)

This type has worst prognosis and it includes poorly differentiated carcinoma or anaplastic carcinoma of the breast. The prognosis is best in type I and worst in type 4 carcinoma.

EXTENT OF THE TUMOR

CLINICAL STAGING OF THE CARCINOMA BREAST

It is physical size of tumors. It is interpreted as clinical staging of the carcinoma breast. If affects the outcome of the treatment. Careful staging of the disease is very important for adequate treatment and prediction of outcome.

Exact size (in centimeters) and site of the tumor should be noted preferably on the diagram.

Palpable lymph glands should be noted and counted. Clinical, biochemical and radiological assessment of the extent of the disease is essential.

One of the great advances in the management of the patients with breast cancer is the development of the clinical staging system.

It establishes criteria to describe the extent of disease and enables the surgeon to identify the patients with advanced local or systemic disease. It helps to estimate the prognosis. It is useful for comparing different treatment results.

There are different staging systems and all assess three elements.

The extent of disease at the primary site.
The presence or absence of regional lymph node metastasis and its extent.
Presence of distant metastasis.

TUMOR, NODES, METASTASIS (TNM)

It is the staging which is mostly accepted now-a-days. It has been modified and simplified.

T (TUMOR)

T 0

present.

N (LYMPH NODES)

N 0
No palpably involved lymph nodes.

N 1
Axillary nodes involved but mobile.

N 2
Axillary nodes involved and fixed.

N 3
Involvement of internal mammary lymph nodes.

N 4
Supra clavicular nodes involvement.
Edema of the arm present.

M (METASTASIS)

M 0
No distant metastasis.

M 1
Metastasis present.
Involvement of the skin beyond the breast means distant metastasis.

STAGE I
(TO, T1, N0, MO)

This includes growths confined to the breast. The involved skin areas (adherent or ulcerated) may be present but these are smaller than the periphery of tumor.
Tumor less than 2 cm in size.
No nodal involvement.
No distant metastasis.

The tumor should not be adherent to the pectoral muscles or chest wall.

STAGE II
(TO, T1 OR T2 and N1, MO)

Tumor size less than 5 cm in diameter but there are affected mobile lymph glands in the axilla of the same side.

Tumor bigger than 5 cms without lymph node involvement. No distant metastasis.

STAGE III
(To, Tl, T2, T3, T4, N2, N3 and MO)

All breast cancers of any size.

Skin involvement or peau-de-orange present in large areas than the tumor itself but these are limited to the breast.
Tumor fixed to pectoral muscles but not to the chest wall.

Axillarly lymph nodes, internal mammary node.

No distant metastasis.

STAGE IV
(TO, T1, T3 & T4, N1, N2, N3. M1)

Skin involvement extends outside the beast as well.
Supraclavicular nodes are involved.
Edema of the army may be present.

Involvement of opposite breast.

CLINICAL FEATURES

False negative results of clinical examination are about 25-30%.

1. LUMP IN THE BREAST

Carcinoma breast usually presents as a painless lump in the breast. The extent of fear and psychological upset by the patient cannot be imagined which is caused by accidental finding of the lump in the breast. All painless lumps of the breast are not carcinomas.

The malignant lump is of variable size. It is hard in consistency. It may be mobile or fixed. Overlying skin of the breast may be adherent showing peau-de-orange or may be freely mobile.

2. NIPPLE DISCHARGE

Blood stained discharge from the nipple is always pathological. It may or may not be associated with the breast lump. It may be the only indication of underlying malignancy.

3. INVERTED (RETRACTED) NIPPLE

Retraction of the nipple is a feature of carcinoma breast. This occurs due to adherence of skin to the tumor under the areola and nipple.

The tumor retraction of one nipple is often associated with carcinoma. Sometimes retraction of the nipple may be congenital and not associated with carcinoma. This is usually bilateral but could be unilateral.

4. ECZEMA OF NIPPLE

This may be the presentation of the Paget's disease of the breast. Usually one side is involved. Bilateral nipple eczema can be presentation of some dermatological lesion.

5. BREAST ULCER

Fungating mass or ulcer of the breast over a lump may be seen. The ulcer is usually hard at its base. The surface is irregular and margins are everted. Size of the ulcer is variable. The ulcer bleeds easily and secondary infection may also be present.

6. METASTATIC FEATURES

Occasionally the carcinoma of the breast presents with features due to presence of secondaries at distant site such as backache or paraplegia due to secondaries in the spine.

Pleural effusion or other chest problems due to secondaries in the chest may be the presenting symptoms.

MANAGEMENT

The logical management of carcinoma breast has following objectives;

SELECTION

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TREATMENT
(To treat the local, loco-regional and systemic disease).

DIAGNOSIS

Simple method for an adequate diagnosis is called triple assessment;

History and clinical examination.
Imaging (ultrasonography & mammography).
Cytohistological examination (FNAC) & Biopsy.

The investigations helps to;

Assess the general condition of patient.
Assess the associated problems (co-morbid factors).
Assess the extent of disease and stage the disease correctly.

INVESTIGATIONS

URINE EXAMINATION

BLOOD EXAMINATION

Hemoglobin percentage.
Total leucocyte count.
Differential leucocyte count.
Sedimentation rate (ESR).
Liver function tests.

RADIOLOGICAL EXAMINATION

X-Ray chest
Skeletal survey

RADIO ISOTOPE SCAN

Bone scintigraphy.
Liver, lung and bone scan (total body scan).

PCR ASSAY

It is used to pick up tumor cells causing occult metastasis in bone marrow cells. Several monoclonal antibodies are used against epithelial mucinous or cytokeratins on the cell surface. These cells are not detectable on routine histopathological examination[21].

ULTRASONOGRAPHY

Ultrasound scan is easily available, simple and non-invasive investigation. It helps in conducting the sonographic guided FNAC and trucut needle biopsy. It picks up the fluid filled lesions of the breast.

It also helps to pick up the metastatic lesions in the liver and lungs.

MAMMOGRAPHY

Major advancement in the treatment of cancer breast has been widespread use of the screening mammography resulting in mortality reduction[7].

Screening by physical examination and mammography can decrease the mortality rate in women over 50 years of age by 30%[8].

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women.

MRI SCAN

The MRI scan is valuable in selected cases of cancer breast as an adjunct to mammography and ultrasonography[10].

It is expensive and not available at every center. It is used to assess the breast lesions in women at high risk.

FINE NEEDLE ASPIRATION CYTOLOGY

Fine needle aspiration and cytology has altered the diagnostic methodology for carcinoma breast. It is the first line investigation for carcinoma breast these days.

It is non-invasive. It is simple. It is performed in the out patient's department. Its sensitivity and specificity is above 95%. It helps in preoperative work up of the patient.

CORE BIOPSY
NEEDLE BIOPSY

Trucut needle biopsy and histopathological examination is confirmatory of the diagnosis. It is an alternative to the excision biopsy. It can be perfor-med in the out patient's department. It can be done under local anaesthesia. Satisfactory core of the tis-sue can be taken for histopathological examination.

EXCISION BIOPSY

Excision biopsy has been the conventional method of confirming the diagnosis of carcinoma of the breast. Although less invasive methods have taken over as first line investigations in the work up of carcinoma of the breast yet in doubtful and difficult cases excision biopsy is the only choice.

The immuno-histochemistry is a simple technique offering more accurate definition of nodal involvement than conventional methods[11].

TREATMENT

Both local and systemic treatment is required to control the disease effectively. Local surgical treatment is essential to get rid of the primary tumor and related lymph glands.

The histological examination of these lymph glands confirms or excludes their involvement.

Various modalities for the treatment of carcinoma of breast are available;

Surgery.
Lymphatic mapping.
Radiotherapy.
Chemotherapy.
Hormonal therapy.
Immunotherapy.
A combination of these modalities.

SURGERY

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This operation has two advantages;

Tumor and all lymph glands are removed and are available for histological assessment.
Postoperative radiotherapy need not to be given.

This operation has many disadvantages such as;

Morbidity is greatly increased.

It has no significant advantage over less radical surgery as far as life span of the patient is concer-ned.

Upper limb edema is a major disability.

MODIFIED RADICAL MASTECTOMY (PATEY'S MASTECTOMY)

This is more popular method than radical breast surgery. The pectoralis major muscle is spared and only pectoralis minor muscle is resected in this operation.

Whole of the breast is removed and the axilla is also cleared of all the lymph glands.

SIMPLE MASTECTOMY

This means removal of the breast tissue and axillary tail. This may or may not be followed by radiotherapy advantages are;

Whole of the tumor is removed.

Morbidity is much less as compared to radical mastectomy.

The serious disadvantage is inability to find out and confirm the lymph node involvement by this procedure.

SIMPLE MASTECTOMY AND PER OPERATIVE LYMPHATIC MAPPING AND SAMPLING

It is improvement of simple mastectomy. This procedure includes simple mastectomy and sampling of the pectoral group of lymph glands.

The enlarged lymph glands in the axilla are also excised and checked histopathologically..

Selective radiotherapy may be added depending upon lymph node involvement.

LUMPECTOMY AND RADIOTHERAPY

It is excision of the breast lump with about 3-5 cms of surrounding and macroscopically healthy tissue. It also includes removal of adherent skin. It is followed by appropriate radiotherapy.

It is a good alternative as it gets rid of the disease process and conserves the breast. It also minimizes the local recurrence and development of invasive carcinoma.

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The advantage of this procedure is that patient doesn't have to loose the breast but this has higher rate of local recurrence.

Radiotherapy is given to minimize local and distant spread. The patient should be followed up very carefully both clinically and with repeated mammograms.

RADIOTHERAPY

This is used as an adjuvant to surgery. Rarely it may be used on its own. It has its own side effects which limit its use. This may be used for ovarian ablation but again oophorectomy is a better method of getting rid of the ovarian function.

CHEMOTHERAPY

Different anti-cancer drugs are used to treat the micro-metastasis and spread of the tumor. This is also used as an adjuvant to surgery.

Neo adjuvant therapy is use of antic-ancer drugs alone or in combination with radiotherapy. It achieves better results before undertaking any surgical procedure. It helps to down stage the tumor.

Different regimens (combination of antimitotic drugs) are being used with variable results such as quadruple therapy.

Following drugs are commonly used;

Methotrexate.
Vincristine.
5fluorouracil.
Adriamycin.
Cyclophosphamide.

CHEMOTHERAPY AND BONE MARROW TRANSPLANT

Navelbine (Vinorelbine or 5-Nor-anhydro-vinblastine is relatively less toxic and has excellent tolerance profile It can be included in the first line combination chemotherapy for breast cancer[20].

High dose chemotherapy and autologous bone marrow transplantation has been used for metastatic carcinoma of breast. It has not shown any added advantage over conventional chemo-therapy[19].

HORMONAL THERAPY

These are best used after oestrogen receptor assay of the excised specimen. Antioesterogen drugs (tamoxifen, Zitazonium and Nolvadex) are being used in patients with cancer breast.

The evidence has been accumulated that chances of recurrence of tumor after hormonal therapy are minimal as compared to radiotherapy and chemotherapy.

Tamoxifen currently is the treatment of

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Herceptin is a monoclonal antibody against a receptor on the breast cancer cell. It is used in stage IV breast cancer. It can be used in combination with chemotherapy for improved response. It binds with the breast cancer cell and stops it from dividing. The antibody binds to the HER-2/neu receptor of the breast cells.

FOLLOW UP

All patients who have been treated for breast cancer by any type of surgery are followed up for rest of their life so that local or distant recurrences is noticed and treated as early as possible.

During first post operative year follow up is performed at quarter yearly intervals and during next two years every six months and afterwards yearly follow up is sufficient.

Self examination by the patient herself have been found to be more useful in early detection of the recurrence. An earlier recurrence which is noticed by the patient is reported and dealt with earlier.

Different studies have shown that routine follow up after potentially curative treatment of breast cancer is not so efficient in the detection of recurrence. But it is highly rated for providing reassurance and reducing anxiety[18].

Prolonged survival has been achieved by;

Evolution of multimodality treatment planning.
Coordinated care.
Use of adjunct chemotherapy[7].

PROGNOSTIC INDICATORS

The prognostic indicators for breast cancer include;

NOTTINGHAM PROGNOSTIC INDEX (NPI)

Notingham prognostic index (NPI) = (0.2 x tumor size in centimeters) + stage + tumor grade

Involved Nodes	Tumor Grade	Score per factor	Prognosis	NPI Score	Survival (15 years)
0	I	1	Good	< 3.4	80%
1-3	II	2	Moderate	3.5-5.4	40%
> 3	III	3	Poor	> 5.4	15%

Example: a 2.5 cm, grade III tumor with 6/12 positive lymph nodes would score NPI 6.5, predicting a poor p

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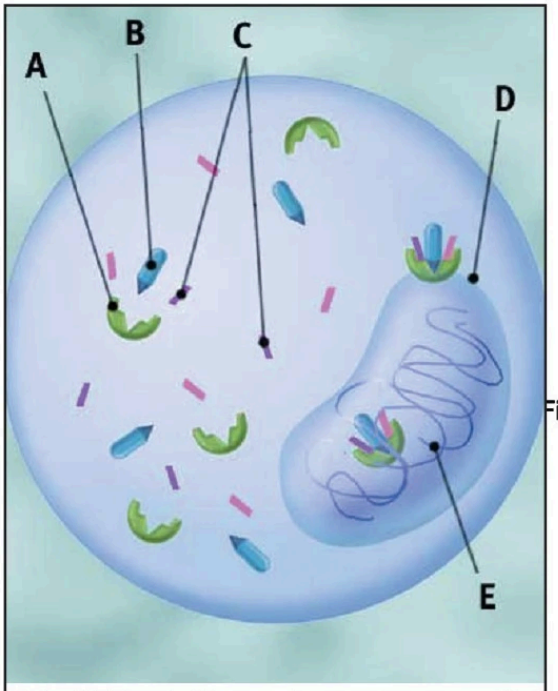


Fig-13.1 Cell with receptors, estrogen, and helper proteins.
(A) Estrogen Receptor (B) Estrogen
(C) Estrogen Helper Proteins (D) Cell nucleus
(E) DNA (genetic material) inside the cell nucleus

Fig-13.3 Peau-de-Orange appearance and nipple retraction
Courtesy Sajid Shiekh, FCPS

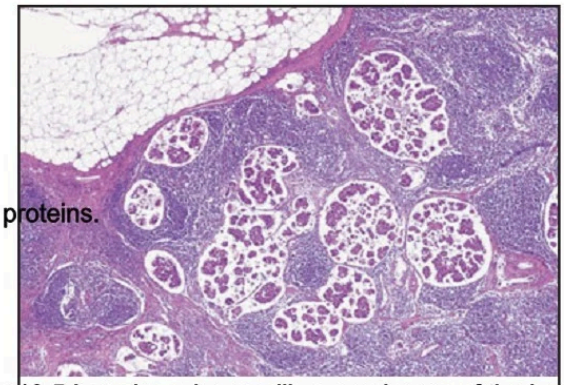


Fig-13.5 Invasive micropapillary carcinoma of the breast.
Lymph node metastasis

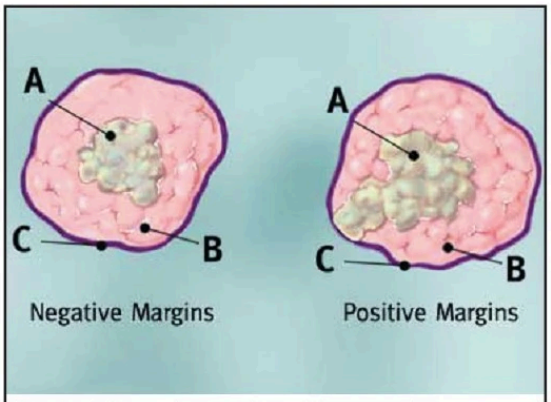
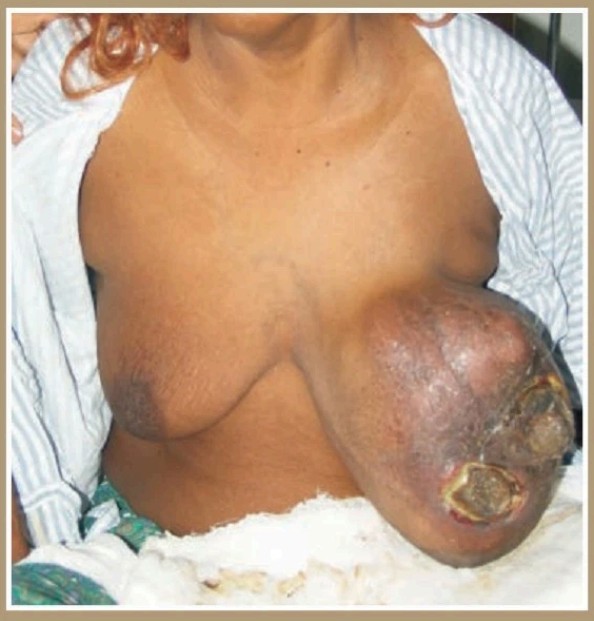


Fig-13.2 Negative and positive margins or margins of resection
(the distance between the tumor and the edge of the tissue)
(A) Cancer Cells
(B) Normal tissue
(C) Ink Marking the Edge

Fig-13.4 Irregular masses right breast (Invasive Carcinoma)

Chapter-14

Metastatic Carcinoma of Breast



Objectives

- To stage the disease.
- To assess the spread of disease with its clinical effects.
- To plan effective management.
- To counsel the patient effectively.

METASTATIC CARCINOMA OF BREAST

Shuja Tahir, FRCS, FCPS

It is the carcinoma of breast which has already spread to distant areas. It is commonly called as advanced carcinoma breast.

Approximately 8% of carcinoma of breast patients present with metastatic disease in the civilized world. The incidence is higher in our part of the world and other less developed countries.

The metastatic disease is seen in many patients after treatment for apparently localized carcinoma breast with or without nodal involvement.

Metastatic metaplastic carcinoma of the breast (MMCB) is well recognized but uncommon aberrant manifestation of poorly differentiated invasive carcinoma containing both epithelial (ductal) and mesenchymal elements as well as a transitional form in between these.

This hetrogenous tumor characteristically contains ductal carcinoma cells mixed with areas of diverse morphologic phenotype, displaying spindle, squamous, chondroid or osseous differentiation. These tumors commonly bypass axillary lymph nodes and present as distant metastasis. It poses diagnostic difficulties at both primary and metastatic site even on FNAC[1].

The patients suffering from metastatic carcinoma of breast are incurable at presentation.

Work up for metastatic disease is essential to assess the extent of disease process and planning the management.

Median survival after diagnosis of metastatic disease of breast is about 02 years but some patients survive upto ten year.

There are two major patterns of disease spread in metastatic breast carcinoma excluding patients with extensive diffuse metastasis.

The patients with positive ER & PR tumors tend to develop, bony metastasis and not brain metastasis.

The patients with negative ER & PR

Chest metastasis and pleural effusion present with breathlessness.

Lungs may have multiple metastasis leading to cough and haemoptysis.

Liver involvement and due to multiple-peritoneal and hepatic metastasis presents with ascities.

Brain involvement presents with headache, convul-sions and others neurological symptoms.

Bony metastasis present with severe pain, fractures, and sometimes even paraplegia due to spinal cord compression.

Bone marrow involvement presents with lethargy, myelo suppression, anaemia and infections.

The clinico-pathological work up for metastatic carcinoma is similar to any kind of breast cancer. Staging of the disease is performed.

Investigations such as urine C/E, blood C/E, liver function tests, renal function tests, x-ray chest, skeletal survey, isotope bone scan, liver scan (ultrasound and CT) are performed.

Tumor markers such as CEA and CA 15-3 are also assessed for monitoring the patient during and after treatment.

The treatment is planned to improve the quality of life and to improve the overall survival. The palliative treatment is given to relieve the symptoms.

MANAGEMENT

Breast carcinoma is a systemic disease. It must be managed and controlled with effective systemic therapy. The patients with metastatic disease have variable problems and require multi disciplinary specialist help.

Every patient with advanced, recurrent or metastatic cancer breast is treated by breast cancer multi-desciplinary team (MDT) which includes oncologist orthopaedics surgeon and pain relief specialist as well as special care nurses for various problems.

OBJECTIVES

To relieve the symptoms.
To improve quality of life of the patient.
To control local spread of the disease.
To control the disease process.

TREATMENT

Appropriate analgesia with or without non-steroidal anti inflammatory drugs are helpful. Opiates can also be used.

Trans-cutaneous electrical stimulations and other methods of pain control may be used.

Immobilization of fractures and mechanical support to the spine is provided to prevent spinal injury and its

tumor is assessed before planning to prescribe hormonal therapy.

A positive estrogen receptor status is associated with good response of over 60% and negative estrogen receptor status is associated with less than 10% response.

The metastatic cancer breast patients with positive receptors may be treated with hormones initially except when advanced liver metastasis is present as the response would be poorer in these patients.

If hormonal treatment is used in these patients, the poor and delayed response may compromise patient's survival. These patients should preferably be managed with chemotherapy.

Patients with estrogen negative receptors should be treated with chemotherapy. Although the response is poor but the control may be achieved for 6-10 months.

Menopausal status and previous chemo and hormonal therapy help to determine the type of hormone to be used. It takes about 6-8 weeks before the response of this treatment becomes obvious.

Good response of hormonal treatment during first line treatment is a good predictor.

Patients who did not receive hormonal therapy initially and are E.R positive may be given hormonal treatment. Others may be offered both poly chemotherapy and hormonal therapy.

Tamoxifen has shown therapeutic advantage when used with chemotherapy in patients of age group 50-69 years. It may prolong survival in advanced disease as well.

Second line hormonal therapy response is approximately 50% of the previous therapy.

A combination of hormones and cytotoxic chemotherapy doesn't improve the response as such. Progesterone or aromatase inhibitors are commonly used as 2nd line hormonal therapy.

Aromatase inhibitors are superior in terms of decreasing morbidity and improving survival than progesterone.

Letrozole 2.5 mg once daily has proved to be more potent suppressor of total body aromatization and plasma estrogen levels in post menopausal women with metastatic breast cancer[3].

RADIOTHERAPY

Adjuvant radiotherapy is used to relieve the pain from bony metastasis. A single dose of 7-8 Gy is helpful. Alternate analgesia is also required for these patients.

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radiotherapy[4].

CYTOTXIC CHEMOTHERAPY

It is used in patients with advanced metastatic disease. It is also used in estrogen receptor negative patients. It is also used after failure of hormone therapy.

A combination of drugs is better than any single chemotherapeutic agent.

(CMF) Cyclophosphamide, Methotraxate, 5 Fluoro-cil is commonly used combination which is very effective according to most of the trials all over world.

The chemo-therapeutic agents are selected after assessing the response of previous therapy, sites of metastatic disease and side effects of the drugs to be used. Commonly used combination of poly chemotherapy is Cyclophosphamide Methotraxate, 5 Fluorocil, vincristine and doxorubicin. The trials have shown 25% response rate with single agent and 50-60% response with combination poly chemotherapy.

Highest response is seen in combination with the use of anthracyclines (adriamycin and epirubicin). But it doesn't increase the survival rate. It only relieves the symptoms.

The therapeutic response is also dependent upon the heterogeneity of cellular population in primary and metastatic breast cancer.

There is prolonged chemotherapy induced response to E.R positive cancer breast patients and those who respond favorably to hormonal therapy. Median duration of response to combination poly chemotherapy is 12-18 months.

Failure to treatment may be changed into remission by use of additional chemotherapeutic agent.

Stage-4 cancer breast patients having complete remission have a median survival upto 32 months.

Dose intensive chemotherapy in combination with transplantation of normal autologous bone marrow cells may show better results and overcome the toxicity factor of cytotoxic drugs.

Locally advanced disease (T3) can be controlled by dose intensive chemotherapy.
(10 times the normal dose)

The tumor cells are killed with larger dose and myelo-suppression can be treated with autologous marrow transplantation. Repeated cycles of therapy are required as the adequate tumor population is not eliminated with this therapy.

The use of hematopoitic growth factor

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antibody to erb B-2 oncogene (expressed in 25% of invasive cancer breast) shows good response. It is used in patients who are HER-2 Neu positive. It is cardiotoxic so it must be used with care.

SYMPTOMATIC TREATMENT

Breast carcinoma is a systemic disease. It must be managed and controlled with effective systemic therapy.

Patients having pleural effusion due to metastatic disease are better relieved with drainage of effusion. It may be required regularly. The frequency of re-effusion can be reduced by instillation of neomycin as anti tumor cytotoxic agent. It may cause pleurodhesis but many times empyema may follow which become troublesome to treat.

Ascities is drained to relieve the abdominal symptoms.

Bisphosphonates help to reduce the morbidity, pain and reduce the number of fractures due to metastatic disease. It can be used as single daily oral dose or a monthly intravenous injection. Its use as a preventive drug against bony metastasis is still to be confirmed.

Surgery for pathological fractures is required. Sometimes surgical fixation is performed prophylactically to avoid pathological fractures and their effects on patients.

Patho-dynamic therapy of extensive chest wall disease may be helpful.

New agents with better response are being developed and evaluated. Taxanes are new chemotherapeutic agents and are helpful against patients not responding to anthracyclines. The response rate is greater than 30%. Vinorelline also shows significant response as second line therapy. Taxanes (Paclitaxel, doetaxel) and vinorelline, topoisomerase inhibitors and new antifolates are also used as second line therapy.

New hormonal treatment includes aromatase inhibitors, Gn RH agonists, anti progestin and new antiestrogens. Biologic therapy targeting growth factors and growth factor receptors such as HER-2/neu and epidermal growth factor receptors have also been developed.

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Fig-14.1 51 year old woman developed recurrent breast carcinoma with an infiltrative plaque spreading from her old surgical scar.

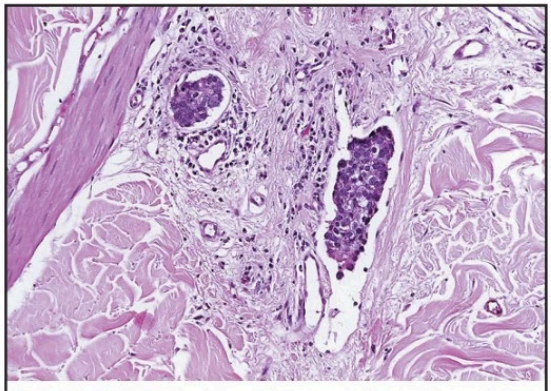

Fig-14.4 Histopathology of recurrent breast carcinoma with an infiltrative plaque spreading from her old surgical scar.

Fig-14.2 Same patient (different view) recurrent breast carcinoma with an infiltrative plaque spreading from her old surgical scar.

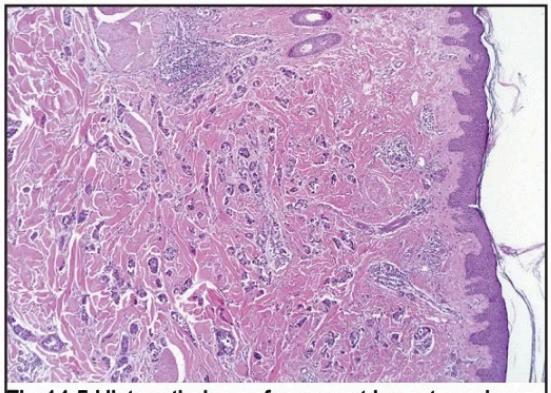

Fig-14.5 Histopathology of recurrent breast carcinoma with an infiltrative plaque spreading from her old surgical scar.

Fig-14.3 Same patient (view from back) recurrent breast carcinoma with an infiltrative plaque spreading from her old surgical scar.

Fig-14.6 75 year old woman with metastatic breast carcinoma. 1 year after mastectomy.

Fig-14.7 Fungating carcinoma breast
Courtesy Sajid Shiekh, FCPS

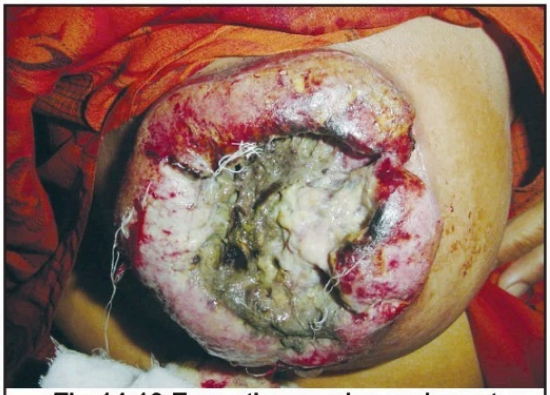

Fig-14.10 Fungating carcinoma breast
Courtesy Sajid Shiekh, FCPS

Fig-14.8 Carcinoma breast (T4)

Fig-14.11 Carcinoma breast with axillary ulceration (T4, N2)

Fig-14.9 Advanced carcinoma breast with lymph edema

Fig-14.12 Carcinoma breast with necrosis around nipple areola compl

Chapter-15

Special Types of Carcinoma Breast

Objectives

- To diagnose the carcinoma breast in special situation.
- To understand the tumor biology in such situation.
- To plan effective management in such situation.
- To counsel the patient effectively.
- To follow up such patients most economically & effectively.

REAST CANCER IN YOUNG WOMEN

Shuja Tahir, FRCS, FCPS

It is the condition when carcinoma of the breast is diagnosed in women at or before 40 years of age.

Breast cancer is very rare in adolescents and very young women.

Less than 1% of all breast cancer cases are seen before the 30 years of age.

Young women have more aggressive presentation of disease at diagnosis, when compared with pre-menopausal elder patients[1].

A young woman may be very young or pre-menopausal (40 years old). There is significant rise in the incidence with increase in age.

Cancer breast incidence in young women is given in the table below.

Age	Incidence/ 100,000 women
Less than 20 years	0.1
20-24	1.4
25-29	8.1
30-34	24.8

The young women's breasts are physiologically more active resulting in cyclic nodularity and thickening.

DIAGNOSIS

TRIPLE ASSESSMENT

Triple assessment is performed for adequate diagnosis.

The self examination and physical examination is more difficult and less helpful in diagnosing breast lesions effectively.

Mammography is done less often in younger women than in older age group.

Even if it is performed, interpretation may be very difficult and less conclusive because of increased radio-density of the breast tissue.

Ultrasound examination of breast is more helpful in younger women suffering from breast cancer.

The disease is diagnosed at a later stage in younger women than in older women.

Breast cancer in young women is more frequently poorly differentiated, oestrogen receptor (E.R) negative, show high lympho-vascular invasion & high proliferating fractions[2].

Young women at potentially high risk of developing breast cancer have germline mutation of BRCA1, BRCA2, Tp53, PTEN. These patients require screening at young age [2].

More aggressive behaviors of cancer breast in younger women can be explained by several biologic factors such as:

- Higher grade & higher expressions of Ki 67.
- Higher occurrence of vascular invasiveness.
- Lesser expression of oestrogen and progesterone receptors [1].

MANAGEMENT PROBLEMS

Young women are vulnerable to emotional distress and psycho social problems & require support [3].

Psychologically the younger women respond badly and show higher level of emotional distress and adjust to the diagnosis with difficulty [2].

Very young women are faced with personal, family, professional and quality of life issues that further complicate the phase of treatment decision making.

The treatment for very young women should be problem based, specific and focused [1].

Breast cancer in young women has special effects of cancer breast and its treatment on;

- Quality of life.
- Child care.
- Future child bearing.
- Marital relations.
- Sexuality.
- Emotional stability.
- Employment.
- Insurability.

Very young women with endocrine-responsive tumors have a higher risk of relapse than elder pre-menopausal patients with similar tumors.

Invasive breast cancer before 35 years of age has more aggressive biological behavior associated with poor prognosis.

The local recurrence rate is as high as 35% in women of less than 30 years of age after lumpectomy and radiation while it is about 0% in women above 50 years of age.

Breast conserving surgery in women under 35 years of age is associated with higher risk of local recurrence.

All young women should be considered at moderate-high risk due to age and should be offered adjuvant therapy.

The implications of possible impaired fertility & premature menopause should be considered before adjuvant therapy [3].

The adjuvant systemic chemotherapy is more effective in pre-menopausal than postmenopausal women. Ovarian ablation occurs within few months of chemotherapy.

Osteoporosis is a serious effect of premature ovarian ablation caused by chemotherapy.

Risk of cardiovascular diseases also increases after lack of oestrogen.

Impaired fertility after adjuvant therapy is a major concern for young breast cancer patients.

Young women may be educated regarding fertility & other issues & research should be diverted for preserving fertility in survivors [3].

Node positive women under the age of 30-35 years have poor prognosis.

Some studies have shown that the younger women of less than 35 years of age suffering from cancer breast show higher survival rates when compared with older women with breast cancer.

Women over 75 years of age showed highest risk of excess deaths [4].

TREATMENT

Treatment for breast cancer in young women is almost similar to treatment given to patients of cancer breast of any age group.

Follow up is also similar to patients of other age group.

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BR-15-B

PREGNANCY ASSOCIATED BREAST CANCER (PABC)

Shuja Tahir, FRCS (Edin), FCPS Pak (Hon)

Cancer breast is common and dreadful malignancy of the females. Women pass through various stages during their life such as infancy, childhood, menarche, adulthood, pregnancy, lactation and menopause. Young women are lucky to have lower incidence of carcinoma breasts than their older counterparts.

Gestational breast cancer or pregnancy associated carcinoma of the breast is an entity which is diagnosed during pregnancy or within one year postpartum[1,7]. It is uncommon but not rare. Carcinoma breast is seen about once in 3000 pregnancies. Pregnancy associated breast carcinoma has poor prognosis. its diagnosis is usually overlooked during pregnancy. The pregnancy associated breast cancer (PABC) is likely to increase with rise in educational level and social status of professional women. More of these women are likely to choose childbearing at later age[2]. Pregnancy related carcinoma breast presents in following situations;

- Breast carcinoma diagnosed during pregnancy;
  - First trimester
  - Second trimester
  - Third trimester
- Breast carcinoma diagnosed after pregnancy during lactation.
- Pregnancy occurring in patients already being treated for carcinoma breast.

There is usually delay in the diagnosis of carcinoma breast in these patients due to physiological changes in the breast during pregnancy and lactation. It is because breasts are enlarged, lumpy and tender during pregnancy & lactation. Early menarche and late menopause are strong negative risk factors for development of carcinoma breast.

Overall menopausal status and age at menopause are significantly associated with breast cancer. A full term pregnancy and early age at first birth are associated with decreased breast cancer risk. Post menopausal women with lactation longer than 48 months have reduced risk of breast cancer. Decreased parity, late age at first birth, early menopause and shorter duration of lactation are important risk factors[5]. The mammary micro environment might become tumor promoting after pregnancy because of the remodeling of the mammary gland to its pre-pregnant state. The remodeling is associated with pro-inflammatory and wound healing mechanisms. It is proposed to support tumor cell dissemination[9].

Fig-15.1 Suspected carcinoma breast in a pregnant woman.

DIAGNOSIS

CLINICAL EXAMINATION

Triple assessment helps in making an accurate diagnosis which is relatively difficult in these patients. All women should be encouraged to practice breast self examination during pregnancy and lactation (II-2B).

The breast examination during antenatal visits may help in early detection[4]. Physicians should screen all women for cancer breast with thorough clinical examination during early pregnancy (III-B). The examination of the breast is also performed during post partum period, if patient is not breast feeding or if she presents with breast symptoms (III-B).

IMAGING

Ultrasound examination of breasts is performed as first line imaging examination in women with suspected breast lesions. Sonography of solid mass with posterior acoustic shadow and marked cystic component may indicate malignancy in pregnant patients[3].

Mammography is usually less helpful because of increased radio density of breast during pregnancy and lactation[3]. Mammogram may appear negative in pregnant women even though the carcinoma si present. It may show calcification, increased skin thickening & asymmetric density. Even mammography of clinically obvious lumps is likely to be misinterpreted during pregnancy.

CYTOHISTOLOGICAL STUDIES

FNAC or even biopsy is used to assess suspicious breast mass in a woman during pregnancy & lactation (II-2A). FNAC may show incorrect results due to presence of hormonal induced atypia in these patients. Core needle/excision biopsy is performed for correct results.

RECEPTOR STUDIES

Tumor receptor studies for estrogen, progesteron, and Her-2-neu receptors are performed before

Fig-15.2 Suspected carcinoma breast in a lactating woman.

80% of cancer breast in pregnant women is estrogen receptor negative.

Interruption of lactation is not necessary while investigating except when nuclear studies are conducted.

Following features are addressed before planning management of breast cancer during pregnancy and lactation;

- The impact of pregnancy and lactation on risk of breast cancer.
- The prognosis of breast cancer diagnosed during pregnancy and lactation.
- The risk of recurrence of breast cancer during subsequent pregnancies.
- Feasibility and impact of breast feeding on prognosis of women with breast cancer. These women have tumors with high histological grade and low frequency of hormonal receptors and high expression of C-erb B-2[6].
- There is good evidence of transient increase in risk of breast cancer in the first 3-4 years after delivery of a single baby (II-2B).
- Subsequently their life time risk is lower than the nulliparous women (II-2B).
- The risk for pre-menopausal breast cancer is reduced with lactation (II-2A).
- This protective effect is best in women with extended periods of breast feeding during their life time (II-2B).
- Women with familial risks could potentially benefit most from breast feeding (II-2C).
- Breast milk is ideal nutrient for new born and breast feeding is a modifiable risk factor. The women should be encouraged for breast feeding(II-2A).

MANAGEMENT PLAN[2]

Once breast cancer is diagnosed during pregnancy or lactation, multi-disciplinary help is used including obstetrician, surgeon, medical and radiation oncologist and breast cancer counselors (II-2A).

When cancer breast is diagnosed during early pregnancy, patient is informed about effects of therapy on fetus and on overall maternal prognosis. It has been shown by many trials that the prognosis is not altered by termination of pregnancy but it can be discussed on its own merits. The patients over 30 years of age should be informed about pre-mature menopause after treatment with chemotherapeutic drugs (II-2C).

No standardized therapeutic interventions have been reported for patients with breast cancer during pregnancy as yet. Various treatment options used presently have not been evaluated for the safety of fetus and efficacy in the mother (the patient).

SURGERY

Surgery remains the gold standard of treatment and modified radical mastectomy and axillary gland dissection is the operation of choice. Breast conserving surgery is not a preferred choice of operation in these patients.

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RADIOTHERAPY

Radiotherapy may be used during first trimester as the fetus is still in the pelvis and can easily be shielded. It is not used in second and third trimester because of danger of irradiation to the fetus.

CHEMOTHERAPY

Chemotherapy can be used in these patients with care. Adjuvant chemotherapy should not be delayed if required but its effects on fetus and future reproductive capabilities should be informed to the patient. (II-2B).

The risks and benefits of early delivery during 3rd trimester should be compared with continuation of pregnancy. Effects of chemotherapy on fetus should be kept in mind (III-B).

Chemotherapy has teratogenic effects on the fetus during first trimester of pregnancy. It can still be used after discussion with the patient about the risks to the fetus and mother. Pregnancy may be terminated or continued as the prognosis is not affected by termination of pregnancy or keeping the pregnancy. It is definitely affected by delay in the required appropriate therapy.

Chemotherapy can be used effectively during second and third trimester of pregnancy with minimal complications of labor and delivery. Commonly following drugs are used with following doses;

- 5 - Flurouracil 1000 mg / m^2
- Doxorubicin 50 mg / m^2
- Cyclophosphomide 500 mg / m^2

These drugs are used at 3-4 weeks interval. The risk of intrauterine growth retardation should be kept in mind following chemotherapy during second and third trimester of pregnancy.

PROTOCOL OF TREATMENT

The chemotherapy is started after complete metastatic work up as given below;

- X-Ray chest (with abdominal shielding in pregnancy)
- PA view and lateral view of both sides.
- Complete blood count.
- Renal function tests
- Liver functions tests
- Ultrasonography

Counseling is done about the risks of chemotherapy to the fetus and mother.

Central venous catheter is passed for long term use.
FAC chemotherapy is used

Day One

- Injection cyclophosphamide 500 mg/m^2 intravenously is given as a single dose.
- Injection doxorubicin 50mg/m^2 is given as continuous infusion over 72 hours.
- Injection 5 fluorouracil 500mg/m^2 is given as a bolus intravenous dose.

Day Four

- Bolus dose of injection 5 fluorouracil is given intravenously.

Three weeks onwards

This course of treatment is repeated after 21 to 28 days during second and third trimester through 37 weeks of gustation[8].

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Patients are monitored with complete blood count, renal function tests and liver function tests before and during the treatment courses.

Side effects such as nausea and vomiting are treated with intravenous ondansetron hydrochloride (zafran) Glaxo. Promethazene or Prochlorperazine tablets.

The fetus is looked after for IUGR which is common after chemotherapy.

SPECIAL ADVICE[2,7]

Women treated for breast cancer may wish to get pregnant. Patients successfully treated for breast cancer can try pregnancy two years after the treatment but patients with advanced cancer breast should be discouraged to get pregnant. All these patients should be informed about possibility of deterioration of prognosis(II-3C).

The women who get pregnant within two years of treatment of carcinoma breast require careful management.

The effects of treatment with high dose chemotherapy and bone marrow transplant with or without radiation therapy on later pregnancies are not known.

Termination of pregnancy in these patients does not seen to improve mother's chances of survival and is not usually a treatment option. It is only considered to avoid teratogenic abnormalities in fetus. It is done with mother's consent after full counseling. It depends upon the age of fetus, stage of disease and the mother's chance of survival[10].

As the recurrence of cancer breast is common in first 2-3 years after diagnosis of cancer breast, the women should be advised to plan pregnancy after three Years. These patients must have oncologic evaluation before such trial. If the patient had cancer breast with positive nodes, she should extend her pregnancy free period to five years (III-C).

The breast feeding does not increase the risk of breast cancer recurrence or development of second primary breast cancer (III-B)[2].

PROGNOSIS

Overall survival is high in both node negative and node positive patients. Five and ten years survival is between 80%-86% and 73%-76%[6].

The pregnancy obscures the disease leading to delay in the diagnosis, hence has poor prognosis. The poor prognosis in these carcinomas is due to age and not due to pregnancy.

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SUMMARY

- Pregnancy associated breast cancer
- Triple assessment
- Special problem assessment
- Risk assessment
- Management plan
- Surgery
- Chemotherapy (treatment protocol)
- Radiotherapy
- Special advice
- Prognosis

POSSIBLE QUESTIONS

- What is pregnancy associated breast cancer?
- Discuss diagnosis?
- Discuss management plan?

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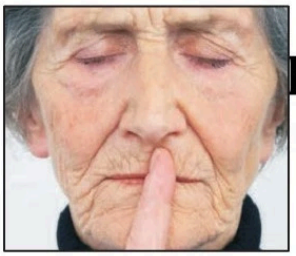

EAST CANCER IN ELDERLY WOMEN

Shuja Tahir, FRCS, FCPS

It is the presence of cancer breast in women aged 65 years or more.

More than 50% patients of carcinoma breast are above 65 years of age[1,6].

A larger proportion presents with a palpable mass. It may be due to less screening of very old women and failure of early detection of disease.

Breast cancer in elderly women is a significant public health problem.

Elderly women have a 6 fold higher breast cancer incidence and 8 fold higher mortality when compared with non elderly women[2].

The number of elderly breast cancer patients is likely to increase in future as the age expectancy increases[2].

The projected increase in number of elderly cancer breast patient is 72% by 2025 in USA[2,3].

The large increase in elderly cancer breast patients requires need for improved preventive and treatment strategies for elderly if the cost of treatment is to be controlled[2].

The problems of age & other age related co-morbid factors may worsen the mortality in these patients.

Infiltrating ductal carcinoma (IDC) is the most common type of carcinoma seen in older women. The old ladies are more likely to have less aggressive tumors which are oestrogen receptor positive[3]. It is 68% of all the tumors. In elderly women it is seen in 77% - 85% of the patients.

The cancer breast in elderly women shows favorable characteristics such as favorable tumor biology, more expression of steroid receptors (estrogen and progesterone receptors), low proliferative rate, good differentiation, normal P53 and low expression of epidermal growth factor[3].

Fig-15.4 Advanced carcinoma breast in an old woman.

As age increases, the incidence of papillary or mucinous carcinoma increases as well.

In women over 70 years of age, estrogen receptor positive cancer breast is more common. It is about 60% - 95%.

The elderly patients of cancer breast usually have less aggressive investigations and treatment leading to delay in diagnosis and poor outcome of treatment.

Mammographic screening in women aged 65 years and above should be established to detect the disease earlier[1].

MANAGEMENT

The improvements in outcome may be achieved by multi-disciplinary management approach involving oncologists, Geriatricians, Surgeons, radio-oncologists, special breast care nurses and social workers[4].

Priorities for breast cancer prevention and control in elderly should be established[2].

Geriatric medicine has established Comprehensive Geriatric Assessment (CGA) to get important information on elderly patients missed by routine clinical examination[4].

The data collected in CGA is of prognostic relevance concerning toxicity of chemotherapy and mortality. The use of CGA improves functional status and mental health of elderly[4].

Careful evaluation of biological prognostic factors, performance status and geriatric parameters such as functional independence, co-morbidities and cognitive function of patient along with determination of her life expectancy and preferences[4].

The treatment decision is made for integerated conservative surgery, radiotherapy and hormo-chemotherapy in otherwise healthy elderly women[5].

Surgery alone or surgery and radiotherapy is the standard treatment for early cancer breast.
(stage I & II).

Lump excision under local anaesthesia may be performed in very old and unfit patients[5,6].

Modified radical mastectomy is offered by some surgeons.

Use of axillary dissection, chemotherapy and radiotherapy is likely to improve the outcome of disease in these patients. Radio therapy should also be offered when indicated[3].

Elderly women can tolerate breast conserving therapy including radiotherapy well and have excellent rates of loco-regional control and disease specific survival[8]. Breast conserving surgery with radiotherapy and mastectomy both can be offered on the preference of the patient[7].

Hormonal therapy is the most effective adjuvant measure for elderly patients with localized disease.

In very old and unfit patients, tamoxifen alone is a suitable treatment. Chemoprevention can be offered on individual basis depending upon the risk ; breast ratio[9].

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Palliative measures can be suggested to frail patients to maximize the balance of benefits and toxicities.

An objective and problem solving approach to the management is most suitable[5].

These women have better 5 years survival rates in stage I & II carcinomas. There is no age related difference in advanced cancer breast.

Elderly women with high bone mineral density (BMD) have an increased risk of breast cancer, especially advanced cancer compared with women with low BMD. There seems to be association between oesteoprosis and invasive breast cancer, two of the most prevalent conditions affecting an older woman's health[10].

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BREAST CANCER IN MALES

Shuja Tahir, FRCS, FCPS

Male breast carcinoma (MBC) is the malignant tumor of the breast in men. It is seen in men over age of 60 years. Carcinoma breast is very rare in men when compared with women suffering from same problem. The information about this problem is limited[1] because of less number of patients.

Only 1% cancer breast occurs in men.
Male to female ratio is 1:125.

There is an association between BRCA2 mutations and male breast cancer specially in those with family history of breast cancer.

The high prevalence of BRCA2 mutations among males should be considered when estimating risk for female relatives[3].

Male breast cancer has biological differences compared with female breast cancer. It occurs late and has poor prognosis because of early spread of the disease.

The early spread is because of less breast tissue, early infiltration to the adjacent tissue in skin and chest wall.

The carcinoma in male breast resembles invasive carcinoma breast of females.
More than 50% of tumors have already spread to distant sites and regional lymph node by the time diagnosis is made.

Gender specific incidence trends differ reflective of female-related changes in surveillance and/or reproductive risk factors.

Its predisposing factors include gynaecomastia and increased endogenous or exogenous oestrogen.

It presents as a lump or an ulcer over the breast. It is most commonly infiltrating ductal carcinoma.

MANAGEMENT

It is similar to female cancer breast. The diagnosis and assessment is done by triple assessment.

Wide excision of the diseased area is usually done by mastectomy.

Neo-adjuvant chemo-radiation may be given in advanced cases to down stage the tumor before surgery.

Adjuvant chemo radiation may also be required in patients with advanced carcinoma breast in males. The volume of breast tissue being small, role of radio therapy has to be reassessed[4].

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It responds to hormonal and chemotherapy but optimal regmines for males are yet undecided due to limited number of patients and lack of possibility of controlled trials.

Its prognosis is not statistically different from that of female invasive ductal carcinoma and invasive lobular carcinoma[1].

It exhibit same prognosis, stage for stage as in females[2].

Fig-15.5 Carcinoma breast in a male.

Fig-15.6 Carcinoma breast in a male.

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Chapter-16

Differential Diagnosis of Breast Lumps

Objectives

- To diagnose the lump in breast.
- To differentiate between various types of lumps.
- To plan appropriate investigations for assessment of the lump.
- To plan adequate management.
- To counsel the patient effectively.
- To plan followup for these patients.

DIFFERENTIAL DIAGNOSIS OF BREAST LUMPS

Shuja Tahir, FRCS, FCPS

Breast is a forbidden territory in our religious society, so most of the lumps are either left undetected or are detected very late. The silly idea in general public that any lump in the breast is cancer is ill conceived.

When an adult woman detects a lump in her breast, usually she gets very apprehensive about its nature. As soon as she consults her doctor for help, the doctor has most important duty to diagnose the lump and its nature correctly and then manage it adequately.

When a patient presents with small lump in the breast, a well organized plan for early diagnosis and correct management is formulated. Triple assessment of breast lesion is performed. It is;

1. Clinical history & examination.
2. Imaging
3. Cyto histological tests

One of the following lesions are to be diagnosed as cause of the problem. Following swellings of breast are seen;

Bilateral swelling of whole breast;

- Pregnancy, Lactation.
- ANDI.
- Hypertrophy.
- Acute mastitis.

The final diagnosis has to be singled out from;

Unilateral breast lumps;

- Fibroadenosis of the newborn.
- Puberty.
- Unilateral hypertrophy.

The isolated lump in a single breast could be;

BENIGN

- Fibroadenoma.
- Simple cyst.
- Galactocele.
- Lipoma.
- Plasma cell mastitis.
- Fat necrosis\Tuberculous abscess.
- Phylloides tumor.

An isolated lump in breast could be;

The lump may not be actually in the breast tissue but may be in its vicinity such as;

Retro-mammary Abscess (from ribs, chronic osteomyelitis, tuberculosis).

- Empyema.
- Chondroma of chest wall.
- Rib deformities.
- Mondor's disease.

TRIPLE ASSESSMENT

It is combination of three sets of observations (clinical, imaging and cystohistological) which have a very high pick up rate in assessment of the nature and extent of the disease. It is very important in case the malignancy is suspected.

Complete history must be written without forgetting the family history, menstrual history, obstetric history and history of breast feeding.

History of the lump must include following information as given by the patient;

- Duration of the appearance.
- Nature (painful or painless).
- Site (four quadrants of the breast).
- Size.
- Consistency.
- Surface.
- Appearance of the surrounding skin.
- Relationship with menstrual cycle.

A structured and careful examination of both the breasts, axilla and clavicular regions is under taken. It is performed in privacy and in the presence of a female attendant or a nurse if the doctor is male.
If is performed in good light and in different positions;

The exact site, size in centimeters, shape, consistency, mobility or fixation of the lump is noted.
Fluctuation and transillumination tests are performed if indicated. Annual or biannual physical examination of the breast is very helpful in women at and above the age of 40 years[1].

Once it is confirmed by history and proper examination that the lump is present, it has to be differentiated very clearly whether the lump is in the chest wall underlying the breast or is in the breast proper.

LUMP BREAST

Similarly a lump lying in the skin overlying the breast has to be differentiated from a lump in the breast proper. Rarely a lump may be present in the accessory breast some where away from the normal breast site.

If the lump is showing signs and symptoms of acute inflammation, the diagnosis of breast abscess can be made safely and treatment can be advised accordingly.

URINE EXAMINATION

Complete urine examination is a simple investigation but gives very valuable information.

BLOOD EXAMINATION

Haemoglobin percentage.
Total leukocyte count.
Differential leukocyte count.
Sedimentation rate.

IMAGING

Sonographic mammography is performed on patients with suspected breast abscess. Pus (fluid) collection is picked up on ultrasonography very clearly and diagnosis is almost confirmed.

It is performed in patients with solid lumps to find out the number and nature of the solid breast lesions.

It is helpful in younger patients because radiomammography is not much helpful due to inability to differentiate between radio dense nature of breast and these lesions.

Middle aged and old patients can be better investigated with radiomammography and lesions may be detected earlier.

CYTOHISTOLOGICAL EXAMINATION

FNAC biopsy is performed for lumps.

Bacteriological examination of the pus aspirate is performed in case of breast abscess.
If signs and symptoms of acute inflammation are not present, cystohistological examination of the lump is arranged and diagnosis is confirmed.
Following lesions are commonly diagnosed in the breast;

Lesions arising in large ducts are;

1. Duct ectasia.
2. Papilloma.
3. Papillary carcinoma.

Lesion arising from terminal duct lobular units are;

1. Cyst.
2. Adenosis.
3. Hyperplasia.
4. Fibro adenoma.
5. Carcinoma.

DUCT PAPILLOMA

It is worm like growth that projects into lactiferous ducts near nipple. It is another benign lump of the breast arising from major duct epithelium close to the nipple. It is a papillary neoplastic growth within the duct. It is found in principal lactiferous ducts or sinus. Usually it is solitary. It may present as friable, delicate, villous and branching growth.

Solitary papillomas usually affect

FNAC, trucut needle or excision biopsy confirms the diagnosis.

Complete excision of the duct system is performed to avoid local recurrence.

UNILATERAL HYPERTROPHY OF THE BREAST
UNILATERAL GYNAECOMASTIA

It is enlargement of a normal breast. The enlarge-ment is uniform. It is more commonly seen in males than females.

It is diagnosed clinically.

Treatment decision and plan is simple. Reassurance or subcutaneous mastectomy can be performed.

Correct size prosthesis may be implanted on patient's choice for good cosmetic reason.

CYST

A breast cyst is collection of fluid in the breast. Cyst results from the enlargement of the breast lobule or lactiferous duct. It is related to altered hormonal stimulation and end-organ response. These often enlarge and become tender before menstrual period starts. The fluid comes from normal secretions. The breasts enlarge and swell towards the end of menstrual cycle.

It can occur at any age after puberty but commonly presents in the perimenopausal years (35-50 years old female).

The cysts can regress spontaneously after menstrual periods or develop after oestrogen replacement therapy[1].
The cyst may demonstrate a thin rim of calcification on mammographic examination. The cyst may occasionally rupture during compression while performing mammography[2].

A cyst can also be clinically diagnosed with reasonable confidence. Usually no edges can be palpated. It is smooth and firm. It moves easily and may be tender. Usually cysts are felt in both breasts and sometimes these are seen at more than one occasion.

It can be easily diagnosed by ultrasound exami-nation. It is confirmed by aspiration. The cyst disappears completely after aspiration.

The patient is followed up every month for the reappearance of the lump. The cyst fluid is cytologically examined and if there is any doubt or the lump does not disappear completely after aspiration or reappears within few days, excision biopsy of the lump is performed.

The patient is followed up for at least 2-3 months after aspiration of the cyst for spontaneous resolution. Excision biopsy is performed in young women with residual breast masses[3].

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leaf like clefts and slits. It can be benign or locally malignant. Occasionally it may be frankly malignant. 15% may metastasize to distant sites.

It distorts the breast and may lead to ulceration of the overlying skin. It may present as a fungating lesion.

Microscopically it is more cellular than other fibroadenomas and there is myxomatous change in the fibrous tissue. It shows increased stromal cellularity, anaplasia and high mitotic activity. Malignant change can occur rarely. Lymph node metastasis is rare as in other sarcomas. It was previously called cystosarcoma phylloides.

This is removed very carefully otherwise recurrence can occur.

GALACTOCELE

It is a rare subareolar cyst presenting in relation with lactation. It is less common problem than thought.

It is commonly seen in women who have recently stopped breast feeding. Occasionally it may occur during lactation as well. It consists of ducts distended with milk.

Aspiration confirms the diagnosis as it drains the milk and the lump disappears. Secondary infection may lead to breast abscess formation.

FNAC, trucut or excision biopsy must be performed in doubtful cases.

HAMARTOMA OF BREAST

The lump is actually a developmental aberration and not a true tumour. It presents as a lump in the breast. It appears as a discrete mass on mammography.

The histological picture is variable and includes;

1. Circumscribed fibro-cysts.
2. Adenolipomas.
3. Fibroadenoma
4. Fat
5. Lobules
6. Cartilage
7. Smooth muscle tissue

Treatment is excision and biopsy[5].

FAT NECROSIS

It is a very rare condition and the lump is often attached to the skin. It is a condition which confuses with carcinoma on clinical examination.

The external features of injury to breast disappear by the time patient presents for treatment. Sometimes the history of injury may be just co-incidental and not the cause of lump. It is painless, round and firm lump or lumps. It is more common in obese female with large breast.

It is due to localized disruption of fat

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FNAC and trucut needle or excision biopsy are confirmatory for the diagnosis.

FIBROADENOMA

It is the most common benign tumor of the female breast. It consists of both fibrous tissue and glandular tissue. It is common before 30 years of age but no age is immune. It has a rubbery feel and moves around easily. It is solid, round and painless. It occurs twice as common in Afro American females than American females. It can enlarge during pregnancy and breast feeding.

A fibroadenoma can be diagnosed clinically with fair degree of certainty.

It may be firm or hard but very mobile lump (breast mouse) within the breast tissue. Its surface is usually smooth and may be lobulated.

The diagnosis is confirmed by FNAC, trucut needle or excision biopsy.

Further management is carried out according to the cytological or histological picture of the lesion.

The giant fibroadenoma grows rapidly and attains large size.

It is bigger than 4-5 cm in diameter. The breast is enlarged, nipple may be displaced, overlying skin is shiny, veins are dilated. It may be present in one breast.

It has higher incidence at two different age groups. It presents at 14-18 years of age and 45-50 years of age.

Treatment is cosmetic enucleation

FIBROADENOSIS

Fibroadenosis is the problem in young women. This can be suspected on clinical examination. The lesions may be present in both the breasts. The feeling of the breast tissue is nodular. There is history of variable degree of tenderness during menstrual cycle. Further confirmation can be done by FNAC, trucut needle or excision biopsy.

CARCINOMA BREAST

Carcinoma of the breast is not so rare in Pakistan as it is thought. A hard lump in the breast with irregular surface could be a malignant lump.

It can be mobile or adherent to the underlying muscle or overlying skin. It may be associated with enlargement of regional lymph glands.

All such lesions should have FNAC trucut needle biopsy or excision biopsy.

Further management is performed according to the extent of disease and histopathological picture.

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Fig-16.1 Fibroadenoma breast (Ultrasound examination)

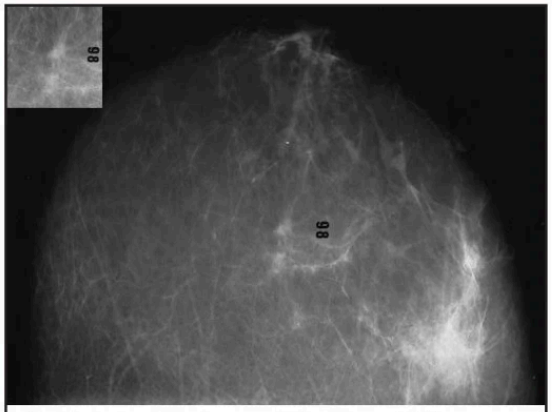


Fig-16.4 Tubular Carcinoma of the Breast (Mammography)

Fig-16.2 Fibroadenotic Cyst (Ultrasound examination)

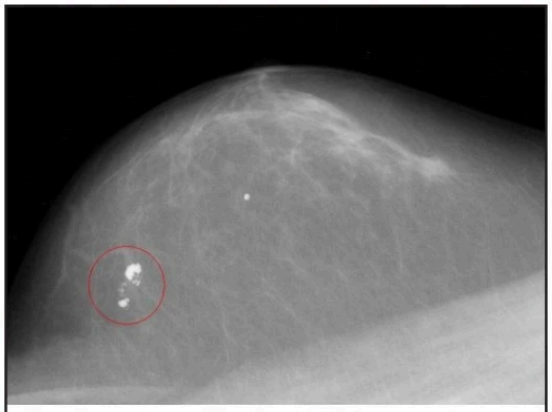


Fig-16.5 Coarse Or Popcorn-like Calcifications (Mammography)

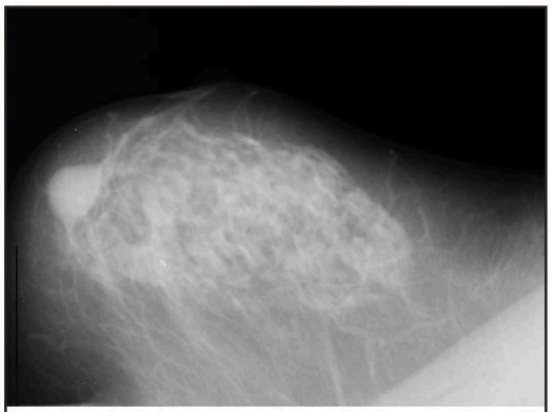


Fig-16.3 Fibroadenoma of breast (Mammography)

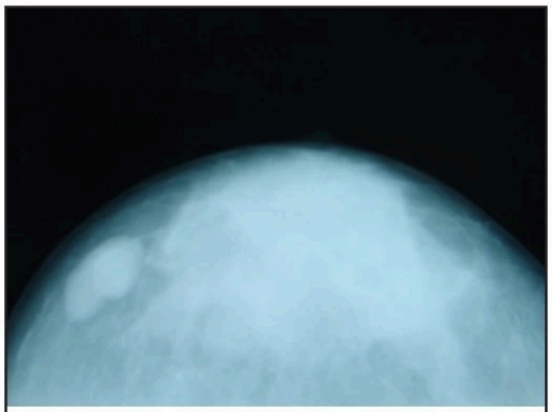
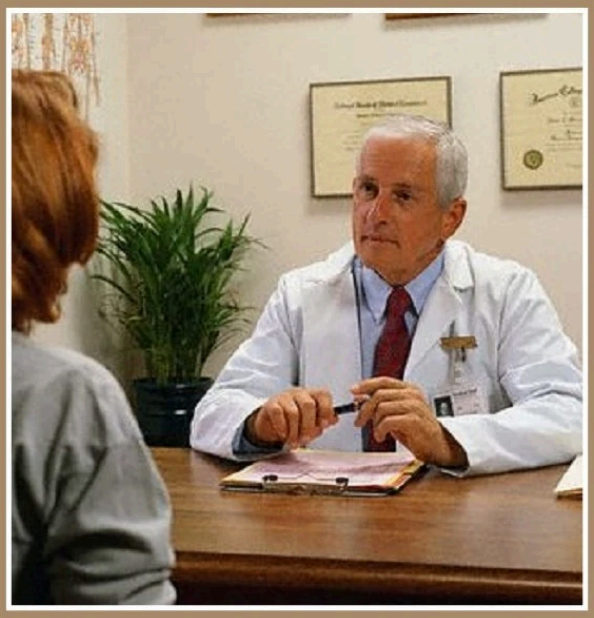


Fig-16.6 Two fibroadenomas of breast (Mammography)

Chapter-17

Counselling



Objectives

- To understand the disease status of the patient.
- To understand the cognitive status of the patient.
- To understand the socio-economic status of the patient.
- To understand the psychological aspects of patient.
- To inform the patient about provisional diagnosis.
- To inform the patient about suggested investigations, their cost and benefit in management.
- To inform the patient about treatment options and their cost, benefits, problems and preference of treating doctor.
- To inform about consequences if not managed properly.
- To inform about the possible complications of treatment.
- To help the patient in making the correct choice.

COUNSELING

Shuja Tahir, FRCS, FCPS
Sohail Ali, FCPS (Psychiatry)
Tariq Mehmood, FCPS (surgery)
Abida Kareem, M.Sc (Clinical Psychology)

Breast carcinoma has such a dreadful reputation socially that most of the women are scared to death even if they suspect or discover a benign or even inflammatory lump in their breast.

They are under such a great psychological strain that information collection and adequate clinical examination becomes very difficult and sometimes even inadequate.

Women who are illiterate, less responsible or unaware of the consequences may even try to sleep over the problem praying for natural relief.

Counseling offers people the opportunity to relieve their distress & improve the ways to manage their health issues regarding cancer breast[1].

Health care providers have to pick up the cases of breast malignancy at the earliest possible time for better treatment.

Certain steps are required to improve the management scenario;

Interaction between patient and the treating doctor, surgeon, oncologist, social worker and psychologist.

Interactive communication among the health care provider and the female sufferers.
Creation of public awareness about the problems related to breast and its ideal management.

The process of counseling starts from the very first visit of the patient to doctor. The patient is very nervous and under great deal of psychological pressure and still undiagnosed. Morale of the patient has fallen immediately after finding out the problem. Restoration of morale helps to improve the management outcome.

The doctor should show concern by listening with patience and allowing the patient to express her feelings. The patient will feel understood after ventilation of emotions. Further counseling should be done after the patient's emotional level is back to normal[3].

The treating doctor has following

Answering the questions of the patient about disease, its treatment, life expectancy, problems related to disease and its treatment, sexual, fertility, pregnancy issues in young women, discomfort to the patient, expected cost of treatment, number of days to be off from work and required socio-economic adjustments in the family.

The general policy of counseling varies from surgeon to surgeon, department to department and country to country depending upon the general awareness of the disease and status of health care and cognitive status of patients.

Some wish to inform the facts very clearly and straight forward rather bluntly. Some have a diplomatic approach.

It is important that one person in the team should be responsible for counseling to avoid misunderstandings between patient and the treating team. Same information is given in the same manner every time otherwise patient will lose confidence on the treating team.

Some patients can face up to the realities of life and death. Some just break up on any bad news. They wish to hear only reassuring news whether its true or just a cover up.

Both policies have advantages and disadvantages. A middle way may be more acceptable in which, the patient may be reassured very optimistically but the facts are given in less harsh and less crude manner.

One doesn't have to inform the patient that “your are going to die within 02 months. Your life can be very miserable. You are going to have lot of pain, vomiting and difficult end of your life”.
Same events can be narrated in a different way such as;

“You know all about the illness. This disease may shorten your life span and may create unacceptable physical problems. It is unfortunate but we have to face the problem with courage and dignity”.

Structured counseling offers a better professional touch. It does not miss a point either and satisfies the patient to maximum extent[3].

It is carried out in five steps;

1. Correction of myths and misconceptions.

2. Counseling is started with an optimistic and realistic tone. The disease process may be discussed more effectively and information is imparted that more than 85% patients with early stage carcinoma breast live almost normal life after adequate treatment. This may be equal to normal life span of majority.

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have better compliance[3].

A balance of advantages and side effects is calculated and correct mode of treatment is selected with patient's consent. The patients accept side effects of therapy in a better way if they are aware and prepared for such problems.

Bilateral mastectomy is increasingly considered as a treatment option for newly diagnosed BRCA1&2 carriers. Patients prefer complete information and BRCA 1&2 testing before surgery to make a decision[2].

Counseling differs as the problems differ in young, pregnant, lactating and older women and male sufferers of the disease.

Young women sufferers have questions about their married life, sexual problems, future pregnancies and future fertility issues.

Pregnant and lactating women wish to ask same questions and more. They wish to know effects of disease and its treatment on fetus and their own future.

Older women have questions about their mobility and quality of life, cost of treatment and life expectancy.

Male breast cancer sufferers are as worried as their counterpart women. The effects are usually different on person to person depending upon the psycho-logical status of the person.

The plan of follow up and appearance of complications and their possible treatment and outcome is also discussed with the patient. Patient becomes fully aware of her problem and responds much carefully and in time.

Patient is also given advice on socio-economic implications of the disease. She is supported and advised to manage her job, family and friends in the best possible manner, one can.

Frequent visits by the social worker, doctor, oncologist, psychiatrist and psychologist are very useful in the care of patient with cancer breast.

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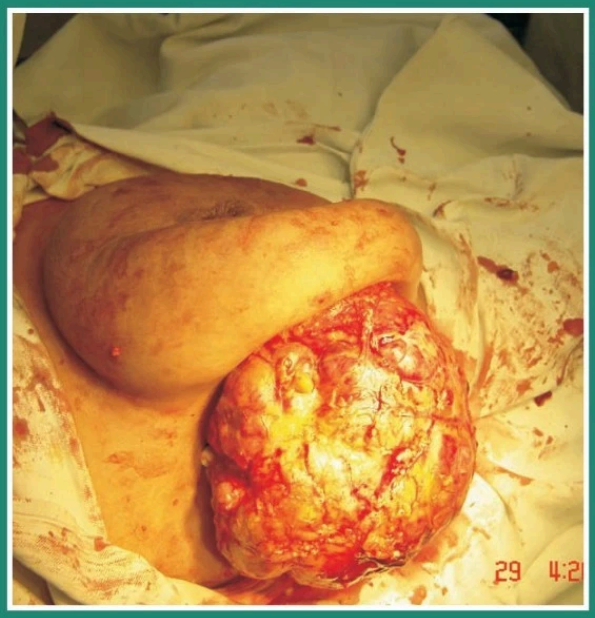
Chapter-18

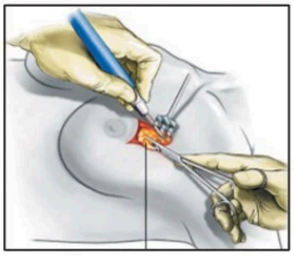
Treatment Modalities - 1
Surgery



Lumpectomy (Wide local Excision)
Segmentectomy Quaderentectomy Hemimastectomy
Simple Mastectomy
Radical Mastectomy
Modified Radical Mastectomy

Objectives

- To offer best available means of surgical management.
- To achieve better cosmetic management results.
- To offer better quality of life after treatment.
- To achieve total cure or maximum palliation.
- To achieve complete excision of the diseased tissue (curative resection).
- To achieve reasonable excision of diseased tissue to relieve symptoms (palliative resection).
- To choose a cosmetically and functionally acceptable incision.
- To keep the front of chest as normal as possible by maintaining the;
  i. Inter breast cleft (cleavage).
  ii. Axillary fold.
  iii. Lower breast fold.



TREATMENT MODALITIES - 1 SURGERY

Shuja Tahir, FRCS, FCPS

Almost 50% of breast cancer is seen in women of 65 years or older. It is also suggested that cancer breast may be more indolent disease in this age group of patients.

Presence of co-morbid factors in this age group and refusal of many patients to aggressive treatment for cancer breast may lead to poor outcome and increased morbidity and mortality.

Patients treated with tamoxifen and radiation therapy had significantly smaller risk of recurrence than those treated with only lumpectomy or those with radiation alone.

This age group of patients is carefully evaluated for adjuvant therapy[1].

Surgery is still one of the most favored treatment modality for breast problems.

Following surgical procedures are commonly used to achieve adequate results;

LUMPECTOMY (WIDE LOCAL EXCISION)

It is the excision of a lump in the breast with a cushion of surrounding healthy tissue. It is performed in a way to leave the breast contour undisturbed and as normal shaped as possible.

INDICATIONS

1. Fibroadenoma breast.
2. Fibroadenosis breast. (Doubtful diagnosis)
3. Early carcinoma of breast. (Breast conserving surgery)
4. Fat necrosis.
5. Galactocele.

PREPARATION

Complete personal and clinical information and observed data is collected such as name, age, sex, menarche, parity, family history, hormones intake, history of malignancy, presence of lump in the breast or nipple discharge.

Baseline investigations for general assessment of the patient such as urine CE, blood CE, sugar, urea, creatinine and electrolytes, are performed. X-ray chest and ECG is also done if indicated.

Specialized investigations to confirm

simple and benign lump in their breast will never change into dreadful malignancy. It is only complete removal of lump which makes them free of fear.

Lumpectomy is planned depending upon its indications for various disease processes alone or it may be associated with hormonal, chemo or radiation therapy in early carcinoma breast.

Proper counseling of the patient is done regarding the procedure, post operative problems, effects of chemotherapy and irradiation and outcome of the surgery. Skin over the breast to be operated is prepared few hours before surgery with the help of non irritating and non allergic antiseptic solution for adequate asepsis (pyodine).

Lumpectomy wound is a clean wound and it does not require any per operative or post operative antibiotic cover. General anaesthesia is selected for better patient compliance, satisfaction and surgical outcome.

INCISIONS

The objectives of incision selection are;

- To achieve adequate exposure.
- To achieve minimum scarring.

Incision is selected with great care. It has to be cosmetically acceptable. Choice of incisions is available for lumps present in different quadrants of breast such as;

CIRCUM AREOLAR INCISION

This incision is selected for lumps near and around the nipple. It gives minimum scar which practically disappears within 3-6 months post operatively. The disadvantages are that it leads to partial anesthesia (loss of sensation) of nipple. But this disadvantage is short lived as the sensations improve after few months.

INFRA MAMMARY INCISION

Hair line/skin crease incision is given over the infra mammary line for inferior peripheral lump which is not in easy access from circum-areolar incision.

GILLIARD THOMAS INCISION

The incision is given just lateral to the anterior axillary line. It can also be used for lump present in the outer part of the breast.

PROCEDURE

Skin and subcutaneous tissue is incised as near as possible to the lump.

Lump is felt and sharp dissection is carried out around the lump leaving few centimeters of healthy tissue. The lump is not held with any tissue forceps or dissecting forceps to avoid trauma to the lump. The adjacent healthy tissue is held during dissection.

(lump bed) is drained with smallest effective drain to avoid haematoma formation. Redivac drain or even smaller semi tube drain may be used.

The skin may be sutured with finest non absorbable suture (Prolene 5/0, 4/0) or the skin is opposed with the help of steri strips to achieve minimum scarring. The sutures or steri strips are removed 7 days post operatively.

FOLLOW UP

The patient is followed up for monitoring the outcome of the surgery and disease process at regular intervals depending upon the diagnosis.

COMPLICATIONS

Haematoma formation.
Infection.
Recurrence of lesion.

SEGMENTECTOMY
QUADERENTECTOMY
HEMIMASTECTOMY

It is the excision of a segment or quadrant of the breast or excision of almost half of the breast. It is the operation devised for breast conservation. Rest of the procedure is similar to wide excision of lump.

SIMPLE MASTECTOMY

It is excision of the whole breast. It inflicts great deal of psychological trauma not only due to loss of breast but because of the fear of the disease biology and complications of the treatment.

INDICATIONS

Carcinoma breast (operable).
Early carcinoma breast.
Minimum carcinoma breast.

COUNSELING

Counseling is of course different as the patient is going to loose the breast. Patient is under psychological pressure due to understanding of disease process requiring mastectomy and associated chemotherapy or radiotherapy and worries about prognosis, life expectancy, effects and complications of the disease and its treatment.

PREPARATION

Patient is prepared in the same way as for any other surgical procedure such as lumpectomy.

Whole of the breast with about 20 cms surrounding area is painted with non irritating and non allergic antiseptic solution.

Skin over ipsilateral axilla and upper part of arm is also prepared with antiseptic solution.

over tumor, nipple and areola of the breast. The transverse scar is minimally visible as it is in hair line. The exposure is adequate. It involves excision of whole breast and axillary tail. It offers reasonable exposure for axillary clearance if so required.

Oblique incisions are used occasionally for upper and outer quadrant tumors when it is not possible to excise the skin over tumor with skin crease incision through a transverse elliptical incision. The cosmetic results are less acceptable being opposite the hair line.

PROCEDURE

Skin and subcutaneous tissue is cut in the elliptical fashion. Both upper and lower flaps are raised with sharp dissection over the breast tissue.

The bleeding points are compressed with help of dry surgical swab and further dissection is carried out to remove the breast without causing any breach in the fascia over pectoralis major and other muscles in front of the chest.

Major bleeding vessels are ligated and compressed with dry surgical swab.

The haemostasis is checked, electric cauterization, compression and ligation of bleeding points help to control the bleeding from bed of the excised breast.

Axillary sampling/clearance is performed if so required.

One or two drains are left in the operation site for proper and complete drainage (Radivac drains) through a separate incision which are preferred for better and secure drainage.
Skin is sutured with silk or prolene or closed with the help of steri strips after adequately opposing the skin.

FOLLOW UP

The patient is followed up as per protocol of follow up for cancer breast followed by the surgical oncologist of the hospital.

ADVANTAGES

Axillary dissection may not be required in early breast carcinoma.
Sentinel node biopsy (SNB) also keeps the dissection minimum.
Skin loss is minimized.
Healing of wound is quicker and suturing is tension free.
There is greater tolerance to radiotherapy as chest wall has most of the muscle layer undisturbed.
Radiotherapy can be started earlier than after radical mastectomy.

SUBCUTANEOUS MASTECTOMY

It is excision of whole breast subcutaneously leaving the skin over breast, nipple areola complex undisturbed.

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scissors and blunt dissection upto nipple where ducts are cut with scissors. The scissors are also used for dissecting the breast over anterior wall of chest.

The breast is brought out of the incision after it has been completely separated anteriorly, posteriorly and peripherally. The dead space is packed with surgical swab for 5-10 minutes to control the bleeding. Bleeding vessels are either diathermized or ligated with fine absorbable suture.

Redivac drain is left in the breast bed (dead space) for drainage under vacuum to avoid haematoma or seroma formation.

The drain is removed 2-3 days later when drainage has ceased and the wound is clean and shows no evidence of haematoma formation or any other complication.

The skin is sutured with non absorbable sutures (silk or prolene). These are removed on 7th post opera-tive day.

COMPLICATIONS

Haematoma.
Seroma.
Wound infection.
Flap necrosis.
Local recurrence.

RADICAL MASTECTOMY

It is the excision of the breast with overlying skin, underlying muscles and draining lymph glands all at the same time and en-bloc.

The classical operation as described by Halstead included following tissues to be removed en-bloc;

1. The breast, skin overlying the tumor including the nipple.
2. Entire system of lymphatic glands in the axilla with lymphatics with fat around them.
3. Sterno-costal part of the pectoralis major muscle, whole of pectoralis minor. Upper part of external oblique muscle of abdomen, anterior divisions of serratus anterior muscle.

INDICATIONS

- Carcinoma breast.
- Same as for mastectomy.

INCISION

The skin and subcutaneous tissue are cut in the line of elliptical incision. The skin flaps are raised to expose whole of pectoralis major, floor of axilla and inferior border of latissimus Dorsi.

An incision is made along the upper border of fascia covering pectoralis major muscle. Sternal fibers are divided near their attachment and it is retracted medially. If required, whole of pectoralis major fibers are divided. The vessels

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and dissection is carried out uptil the posterior axillary wall muscles(subcapularis, teres major and latissmus dorsi) and serratus anterior on the medial wall. All fascial, fatty and glandular tissue are removed. The nerve to serratus anterior is identified and preserved. A hot wet surgical towel is used to compress the dissection area to control bleeding during surgery.

The skin flaps, fascia fat and the breast with underlying muscles are sharply dissected out from above the ribs and costal cartilages.

Perforating branches of internal mammary are seen while dissecting sternum. These vessels are identified, ligated and cut to avoid severe blood loss. The upper part of rectus sheath is removed in the line of incision. Sternal fibers of pectoralis major muscle are raised and deep fascia is divided along with the line of sternal margin on the opposite side.

After excision of breast and all tissue en bloc, the bed of mastectomy is compressed with hot wet towel. Then any remaining fatty or glandular tissue is looked for and removed.

Major vessels are carefully ligated. Smaller vessels can be coagulated with electrical diathermy. The skin flaps are sutured without any tension. Skin graft may be used if complete skin cover is not easily possible without tension.

24 fr size tube drain is left to drain the wound adequately. Redivac drain can also be used. Soft dressing with reasonable padding is applied to avoid chest compression.

A tight dressing never prevents haematoma formation, it only causes discomfort and respiratory embarrassment.

The patient is looked after post operatively. The drain is usually removed after drainage has stopped and it takes about 4-5 days after surgery and it takes seven to eight days for the skin wound to heal. The sutures are removed after that.

COMPLICATIONS

1. Bleeding.
2. Haematoma formation.
3. Painful limb movements.
4. Upper limb edema.

MODIFIED RADICAL MASTECTOMY

The radical mastectomy was found to be a mutilating operation with lot of physical and psychiatric complications. It provided hardly any significant advantage in the cure of dreadful carcinoma of breast when compared with conservative surgical options.

The credibility of this aggressive approach was challenged and modifications were advised. Patey and others advocated a modified radical

COMPLICATIONS

1. Bleeding.
2. Haematoma formation.
3. Painful limb movements.
4. Upper limb edema.

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Fig-18.1 Preparation of breast (Giantfibroadenoma) for surgery

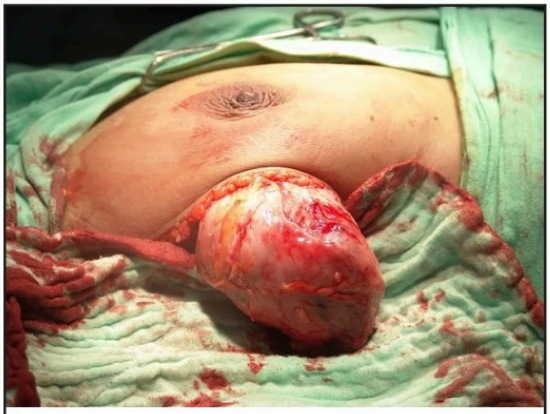

Fig-18.4 Excision of Giantfibroadenoma right breast

Fig-18.2 Cosmetic incision (Gillard Thomas) for excision of giantfibroadenoma

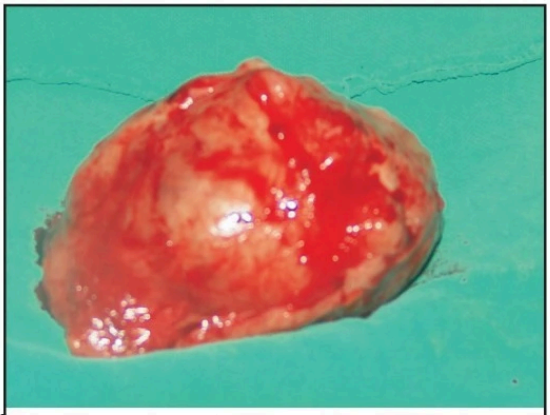

Fig-18.5 Excised specimen of Giantfibroadenoma breast

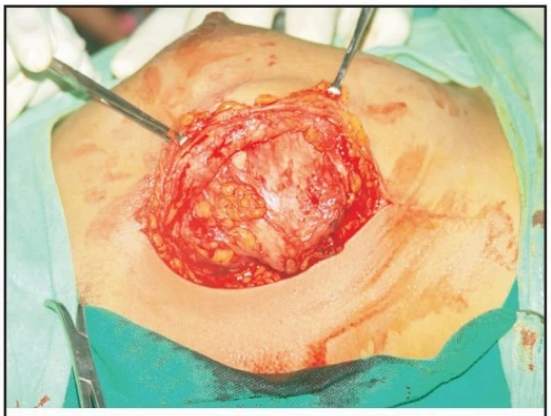

Fig-18.3 Excision of Giantfibroadenoma right breast in progress

Fig-18.6 Excision of fibroadenoma breast through circum areolar incision

Chapter-19

Radiotherapy Treatment Modalities - 2

Neoadjuvant Radiotherapy
Adjuvant Radiotherapy
Palliative Radiotherapy
Curative or Radical Radiotherapy
Brachytherapy

Objectives

- To be used as neoadjuvant therapy in malignancy.
- To control the local recurrence after surgical treatment of malignancy.
- To be used as adjuvant therapy after surgery.
- To be used as palliative treatment for advanced

RADIOTHERAPY TREATMENT MODALITIES - 2

Shuja Tahir, FRCS, FCPS

Radiotherapy is a very important treatment modality for cancer breast. It involves use of ionizing radiation to kill the neoplastic cells.

Its objective is to deliver a focused and measured dose of radiation to the tumor mass to achieve complete or near complete ablation of tumor tissue and to avoid damage to the surrounding healthy tissue.

Radiotherapy is being used to treat breast cancer since end of 19th century. Initially the tumor used to regress but damage to adjacent healthy tissue used to be excessive and unacceptable. Technical hazards and radiation damage to the staff were other serious problems.

About half a century ago, megavoltage radiation delivering machines were developed. These help to deposit radiation in tissues at required depth and avoid excessive skin necrosis.

Linear accelerators are now used to produce high energy x-rays (electrons are accelerated down a cylindrical wave guide and are bombarded at a fixed target at the end to produce x-rays).

High energy electrons can be produced for treatment in some machines. Electrons have the advantage of limiting the depth of penetration by varying the electronic energy.

The use of CT planning and computer software technological developments have improved focused radiation dose delivery to the malignant tissue. It has also reduced the risk of damage to surrounding normal tissue.

The radiotherapy can be used alone or in combination with other modalities to treat cancer breast. It can be used as;

- Neo-adjuvant radiotherapy.
- Adjuvant radiotherapy.
- Palliative radiotherapy.
- Curative radiotherapy.

NEOADJUVANT RADIOTHERAPY

It is the use of radiotherapy in cancer breast when tumor is inoperable or when breast conserving surgery is required. The cancer breast is down

1. To make the tumor resectable by downsizing the tumor (down staging the tumor).
2. To sterilize the cells pre operatively so that after surgery they may not be seeded.
3. To eradicate the lymphatic spread or subclinical disease outside resection margins.

The main disadvantages of pre-operative radiotherapy are;

1. It interferes with normal healing although it is minimal with doses of 45 – 50 Gy in 2 fractions.
2. Alteration of pathology results may lead to alteration of further management.

ADJUVANT RADIOTHERAPY

It is the use of radiotherapy alone or in combination with chemotherapy for the treatment of cancer breast after surgery has been performed. The Outcome of management of carcinoma breast is improved after adjuvant radiotherapy. It helps to eradicate possible subclinical residual disease and reduces the risk of local and distant recurrence.

Accurate post operative localization of the radiotherapy area helps to provide better, focused radiotherapy.

Adjuvant radiotherapy to chest wall and nodal groups after mastectomy is used in women of high risk.

Indications of adjuvant radiotherapy include;

- Deep margin involvement in tumor.
- Skin involvement.
- Size of tumor.
- Wide spread lympho vascular involvement.
- 4 or more positive axillary nodes.

Determination of optimal patient for adjuvant radiation therapy is highly individualized and had risk adjusted approach.

Four issues are considered;

- Evaluation of risk of relapse.
- Concurrence with results of trials.
- Therapeutic ratio.
- Patient preference.

The adjuvant therapy is useful in patients diagnosed with invasive breast cancer of more than 1 cm size in improving disease-free survival and overall survival.

DISADVANTAGE

It requires higher doses of radiation

Delay in radiotherapy in cases of wound infection and poor healing may lead to recurrence of tumor locally.

It has no effect on tumor seeding at the time of surgery.

is not possible. Radiotherapy is used to relieve the symptoms by down staging the tumor. There are some degree of side effects of radiotherapy but these are minimized by controlled dose delivery of radiation to the tumor.

CURATIVE OR RADICAL RADIOTHERAPY

It is the use of radiotherapy for treatment of early lesions of cancer breast. It is used when there is a calculated chance of permanent tumor control and long term survival after high dose radiotherapy.

Side effects are accepted as the ultimate cure is expected.

PHYSICAL PROPERTIES OF IONIZING RADIATION

The radiation used for radiotherapy can be electromagnetic or particulate. Commonly used x-rays and gamma-rays are part of continuous electromagnetic spectrum. These are supposed to be packs of energy photons.

The physical properties of x-rays and gamma-rays are similar but these are produced differently. X-rays are produced electrically in the x-ray tube. Gamma-rays are emitted from radiation of substances while these decay.

Particulate radiation includes electrons, neutrons, protons and heavy charged particles.

Radiation becomes variable in depth of penetration and energy emission.

Superficial x rays (10 – 125 Kev) deposit most of their energy in the skin and subcutaneous tissue. These are used for skin and subcutaneous tissue malignancies (recurrence of tumor in skin).

The megavoltage therapy (4 – 24 MV) deposits energy in the deeper tissue sparing the skin. Deep seated tumors are treated and overlying skin is spared of damage.

Electrons are usually used to treat superficial tumors because these don't penetrate deeply. Their dose falls on deep penetration.

The radiation dose is described in terms of the amount of energy (Joules) absorbed per unit mass (Kg). It is measured in grays (J/Kg)

BIOLOGICAL EFFECTS OF IONIZING RADIATION

DNA of the neoplastic cells is the target of radiation. Ionizing radiation can have direct action on DNA or indirect through an intermediary. Most of the energy deposited, is absorbed initially in water which produces free radicals (molecules with impaired electrons).

These free radicals react with cellular

NORMAL TISSUE RADIATION BIOLOGY

The response of radiation depends on the degree of differentiation of the cells. The terminally differentiated cells, such as muscles and nerves are more resistant to radiation. It takes months and years to affect slowly proliferating tissue.

Bone marrow and reproductive organs can be damaged by relatively low doses of radiation. The toxicity from radiotherapy may have immediate or late side effects.

Immediate effects are seen within days or few weeks. These effects are severe and seen when treatment is given in shorter period. Typical side effects are mucositis, skin erythema, and bone marrow suppression.

Late effects are dependent upon total dose of radiation and its fractionation. These effects tend to be dose limiting factor in treatment schedule.

These effects include necrosis, fibrosis and chronic ulceration. Further radiation is avoided to the areas showing these effects as it may cause excessive toxicity.

THERAPEUTIC INDEX

It is the tumor response for a fixed level of normal tissue damage. The gain in local tumor control is balanced against the rise of normal tissue toxicity.

Three dimensional, conventional, intensity-modulated radiotherapy allows smaller volumes to be treated. It achieves a gain in the therapeutic index.

FRACTIONATION

A higher local dose can be tolerated by giving smaller repeated doses of radiation than a single larger dose. It allows normal tissue to repair and repopulate before further radiation. Higher total doses increase the probability of tumor control.

Fractionation describes the number and size of radiation treatments. The standard fractionation schedule is 1.8-2 Gy/day, 5 days a week.

Unscheduled interruptions in radical treatment allow repopulation of tumor cells and loss of tumor control. It should be avoided.

HYPO-FRACTIONATION

It is when small number of relatively large fractions are given.

ACCELERATED FRACTIONATION

It is when a standard dose fraction is given over a shorter treatment time (more than 5 fractions/week).

HYPER FRACTIONATION

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It depends upon the anatomical site of the tumor, its histological picture and staging. The target volume is defined in three steps;

- Gross Tumor Volume (GTV).

It includes all gross tumor.

- Clinical Target Volume (CTV).

It includes gross tumor volume and microscopic spread.

- Planning Target Volume (PTV).

It includes CTV and margin to allow for daily variation in treatment set up.

The decision for treatment is made after full consultation with physicist and dosimeterist. Best distribution is selected to gain homogenecity within the target volume to reduce toxicity to normal tissue.

Whole treatment plan is tested or simulated to ensure correct treatment area. Marking and immobilization ensures daily treatment volumes.

Radiotherapy can eradicate the tumor. Its effectivity depends upon the vascularity of the tumor. It fails to be effective in hypoxic areas of the tumor.

COMBINATION THERAPY

Lumpectomy followed by radiotherapy is an effective treatment for non invasive carcinoma of breast (ductal carcinoma in situ) and invasive carcinoma breast. In early breast cancer, shorter radiation schedules are as efficient for local control and short term cosmetic results as traditional fractionation regimens.

Sentinel lymph gland biopsy and regional radiation is offered to patients with positive nodes[3].

Low dose-rate implants upto 60 Gy are well tolerated. The post radiotherapy fibrosis increases upto 25% after implant dose of 60 Gy. The dose calculation requires further studies[2].

Indications for boost treatment can include;

- Close resection margins (less then 01 cms).
- Extensive in situ diseases.
- Vascular invasions.
- Grade III tumor histology.

Survival after breast conservation surgery and radiotherapy is comparable to mastectomy. Adjuvant radiotherapy reduces local recurrence upto 2/3[rd].

Radiation therapy after high dose chemotherapy provides excellent local control rates without excessive toxicity. Delaying the start of radiotherapy until recovery from high-dose-chemotherapy side effects doesn't seem to increase local failure rates[6].

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Estrogen receptor assessment is valuable for predicting prognosis of early stage breast cancer patients treated with BCS and radiotherapy[4].

The benefits of hormonal therapy are limited to patients with positive estrogen receptors. Anthracyclines show improvements in patients with positive nodes[5].

BRACHY THERAPY

It involves intra cavity irradiation using radio-active sources placed in the tissue cavity near the tumor or interstitial radiation using radio-active seeds, needles or wires implanted directly into tumor tissue.

Breast conserving treatment leads to excellent long term results in terms of local control and marking classical risk factors.

High dose and large-volume interstitial brachy-therapy is superior to breast conserving treatment without brachytherapy[7].

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Chapter-20

Treatment Modalities - 3
Hormonal Therapy

Objectives

- To understand the effects of various hormones on cancer breast patients.
- To treat the cancer breast patients with hormonal manipulation.
- To use the hormonal therapy as neoadjuvant or adjuvant therapy either alone or in combination with other therapies for cancer breast.

TREATMENT MODALITIES - 3 HORMONAL THERAPY

Shuja Tahir, FRCS, FCPS

Hormonal therapy for cancer breast is use of hormones for its treatment. The relationship between hormones and various problems of breast has been known for a long time.

The influence of hormones on tumor tissue was discovered over a century ago.

Sir George Beatson showed regression of inoperable breast cancer after oophorectomy during 1896.

Surgical ablation remained major form of endocrine therapy for next fifty years.

A rational basis for the use of hormone manipulation in breast cancer treatment could not be formed due to lack of knowledge of how hormones or hormonal antagonists act on cancer cells[1].

The hormonal therapy became popular with the understanding of various aspects of effects of hormones on their target organs.

STEROID HORMONES & THEIR RECEPTORS

Receptor proteins for steroid hormones are present in the cytoplasm and nucleus. Interaction between hormone and its receptor modifies DNA activity, cell growth and cell division. The events for the steroids effects on cell proliferation are as;

- Free, non protein bound hormone crosses the cell membrane.
- Hormone links to cytoplasmic receptor protein and forms a complex in cytoplasm or nucleus.
- Hormone receptor complex binds to a nuclear protein which controls DNA activity.
- An increase in RNA polymerase activity through production of mRNA leads to cytoplasmic protein production.
- DNA synthesis occurs in 24 hours followed by cell division.
- The production and activation of hormones can be reduced by surgical, radio therapeutic or chemical ablation.
- The binding of hormone to its receptor can be prevented even when it has entered the cell by competitive inhibitors or reduction in production of receptors.

data such as age, menopausal status, general condition of the patient, grading and staging of the disease.

The receptors may not be functionally active even if these are present.

All women suffering from carcinoma breast must have oestrogen receptor status assessed for adequate immediate and future management.

Hormonal treatment is used as adjuvant in advanced stages of carcinoma breast.

All patients with positive oestrogen receptors receive tamoxifen for five years. This treatment is also given to patients with advanced carcinoma breast and positive oestrogen receptors as palliative treatment.

The objective response to initial hormonal treatment in these patients is 65- 75% for 12- 15 months.

The response to 2nd and 3rd line hormonal treatment in patients with oestrogen receptor negative patients is only 5%.

OVARIAN ABLATION

Younger women (less than 35 years of age) with carcinoma breast and oestrogen receptor positive status respond to oophorectomy very well. The patients with oestrogen receptor negative status are not recommended for oophorectomy. Surgical oophorectomy has a rapid response when compared with radio-therapeutic or chemical ablation otherwise frequency and duration of response are same.

LHRH is a decapeptide released from hypothalamus to act on pituitary to produce LH and FSH.

LHRH analogues produce medical equivalent of oophorectomy within two months of administration. These provide response rate similar to surgical oophorectomy but it has an advantage of being reversible in women who wish to stay fertile.

Its combination with tamoxifen provides complete oestrogen block in pre menopausal women thus giving it a much superior role.

ANTI OESTROGENS

Tamoxifen is an anti oestrogen. It is effective in both pre and post menopausal women with carcinoma breast.

It is used as first line treatment for patients with hormone sensitive metastatic carcinoma breast. It is relatively less toxic.

It is non steroidal anti oestrogen which competes with circulating oestrogens for binding at receptors. The blocking effect leads to some of its anti

The oestrogens are mainly produced by peripheral conversion of adrenal androgens in muscle, liver and fat in post menopausal women. These are mediated by aromatase enzymes. Breast tissue also contains aromatase and can synthesize oestrogen. Aromatase inhibition can exert anti-tumor effect in carcinoma breast.

Aminoglutethamide and anastrozole have achieved response rate of about 30% in post menopausal women progressing on tamoxifen. Anastrozole is used as first line treatment due to lower toxic effects.

Progestogens and anabolic steroids are relatively less helpful in the treatment of post menopausal patients with carcinoma breast due to their toxic effects. Flavopiridol is cyclin dependent kinase inhibitor. It disrupts the cell cycle and is an important therapeutic strategy. It causes cell cycle arrest, induces apoptosis, inhibits angiogenesis and potentiates effects of chemotherapy[2].

HRT AND BREAST CANCER

The menopausal women with diagnosed carcinoma breast or without carcinoma breast require Hormone Replacement Therapy to prevent/ treat/avoid menopausal symptoms and osteoprosis and associated morbidity and mortality.

Estrogen use increases the risk of breast cancer or combined hormone therapy increases the risk of carcinoma breast in females is not supported by various studies. The long term use of these hormones (more than 15 years) may increase the risk slightly[3].

Use of HRT does not increase the risk of carcinoma breast recurrence. It does not shorten life expectancy in women on treatment for primary invasive carcinoma breast[4].

Approximately half of breast cancers occur in women of 65 years or older. The cancer breast may be more indolent disease in this group of patients. It may be as a result of comorbid conditions and less aggressive treatment for this age group patients.

The patients treated with tamoxifen and radiation therapy has significantly smaller risk of recurrences than those treated surgically alone (lumpectomy) or radiation alone[5].

HRT use for menopausal symptoms by women treated for primary invasive breast cancer is not associated with an increased risk of breast cancer recurrence or shortened life expectancy.

Anastrozole is an effective and well tolerated option for the treatment of post menopausal patients with hormone sensitive early breast cancer. Longer follow up is required for final

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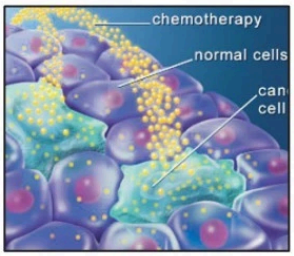
Chapter-21

Treatment Modalities - 4 Chemotherapy

Objectives

- To use chemical agents to destroy the malignant cells selectively.
- To use chemical agents to palliate malignancy.
- To use chemical agents to downstage the tumor before surgery (Neo-adjuvant).
- To use chemical agents after surgical excision of malignancy to prevent spread (adjuvant).
- To use chemical agents with hormones & radiation to enhance the anti-



TREATMENT MODALITIES - 4 CHEMOTHERAPY

Shuja Tahir, FRCS, FCPS
Faisal Bilal Lodhi, FCPS

Chemotherapy is the treatment of breast cancer with various chemical agents commonly used in combination. It is also called anti-cancer chemotherapy or cytotoxic drug therapy.

There have been a great deal of developments in cancer chemotherapy over last few years. Very extensive research trials have been conducted all over the world to assess the outcome of treatment after use of various combinations of these drugs.

More and more cytotoxic drugs have been developed and made available for human use. Their toxicity has been reduced and new techniques have been developed for the administration of these drugs.

Better understanding of cancer biology and availability of these drugs have improved the outcome of breast cancer. Overall survival of breast carcinoma patients has improved.

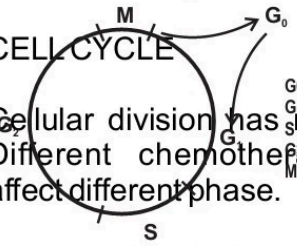
Understanding of tumor biology has helped to target malignant cells selectively.

Unfortunately these drugs are expensive to the extent that most of the public fails to use the drugs due to economic problems, the cost/benefit ratio of these drugs is not always justifiable to majority of our public.
Recent cytotoxic drugs “Taxanes” (taxol and taxotere) are so expensive (more than 100,000 rupees per dose) that it is difficult to use these with their cost/benefit ratio. These may be used as second line therapy for advanced or recurrent breast carcinoma.

The chemotherapy is used to destroy tumor cells selectively. It is achieved by specific growth characteristics of most of the tumors.

The understanding of cellular cycle is important to plan the chemotherapy most effectively.

CELL CYCLE



Cellular division has multiple phases. Different chemotherapeutic agents affect different phase.

G-o is a resting phase outside the cell

cells are in **G-o** phase and drug penetration is less reliable. Moreover the cells in G-o are resistant to effects of cytotoxic drugs.

The faster the cells are growing. It is more likely that cytotoxic drugs can "catch" these (kill these).

It also accounts for chemotoxicity on rapidly growing normal tissues (e.g Gastrointestinal mucosa and Bone marrow).

Large tumors are relatively unresponsive to chemo-therapy due to incomplete penetration.

Most drugs kill a fixed proportion of cells rather than fixed number. Different drugs act during different phases of the cell cycle. Various combinations of drugs are more likely to be effective than single drug and have less toxic effects.

Cell synthesizing DNA go through a regular cycle with different phases. Most of the chemotherapy drugs cause DNA damage through various processes;

Disruption of cell cycle check points.
Growth factors.
Growth factor receptors.
Signal transduction pathways.
Cell death by apoptosis.

Chemotherapeutic agents are of various types;

NON PHASE DEPENDENT DRUGS

These are the chemotherapeutic agents which don't effect any special phase of cell division.

These kill cells exponentially with increasing dose.
These are equally toxic for cell within the cell cycle or G-o phase.

Examples include;

Alkylating agents.
Cyclophosphamide.
Cisplatin.
5-Fluorouracil.
Anthracyclines.
Doxorubicin.

PHASE DEPENDENT DRUGS

These kill cells at a lower dose.
These act within a specific phase of the cell cycle.

Example include;

i. Methotrexate
ii. Vinca alkaloids – vincristin, vinblastine

Breast carcinoma shows significant response when treated with chemotherapy.

ALKYLATING AGENTS

These are chemically reactive drugs.

Carmustine.
Lomustine.
Cisplatin

Cisplatin inhibits DNA synthesis by cross linking DNA strands.

ANTI-METABOLIC AGENTS

These are anti cancer drugs which resemble naturally occurring purines , pyramidines and nucleic acids. These inhibit key enzymes involved in DNA synthesis.

Purine analogues.
Azathioprines.
6 Mercaptopurines.
Fludardine.

Methotraxate is an antifolate drug. It stops DNA synthesis by inhibiting the activity of dihydrofolate reductase. It leads to cell death. The biochemical toxicity can be reversed by restoring intracellular folate (by administering folic acid) and normal tissue may be saved.

MITOTIC INHIBITORS
TUBULIN BINDING DRUGS

Tubulin is normal and basic subunit of microtubules and has many important cell functions such as spindle formation and chromosome migration during cellular division.

Vinca alkaloids and taxanes belong to this group of drugs.

Vinca alkaloids bind to tublin and inhibit the metaphase of mitosis.
TOPOISOMERASE INHIBITORS

It is a group of enzymes which allow unwinding and uncoiling of super coiled DNA

Topoisomerase-I preferentially binds to double stranded DNA and causes a single strand break.

Topoisomerase-II binds covalently to comple-mentary strands of double strand DNA cleaving both strands.

ANTI TUMOR ANTIBIOTICS

These act differently by DNA cross linking and topoisomerase inhibition. These lead to alteration of cell membrane function.

PYRAMIDINE ANALOGUES

Gemcitabine.
5 Fluorouracil.
Capecitabine.
Methotrexate.
Reltitrexed.
Vincristine.
Vindesine.
Vinblastine.
Vinorelbine.

TAXANES

Paclitaxal
Docetaxel

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TOPOISOMERASE II INHIBITORS

Etoposide.
Teniposide.

ANTI TUMOR ANTIBIOTICS

Anthracyclines.
Doxorubicin
It inhibits RNA synthesis by intercalating between DNA base pairs.

Epirubucin.
Daunorubacin.
Idarubacin.

Anthracenediones
Mitoxantrone.
Bleomycin
It inhibits DNA polymerase causing breakage of single stranded DNA.

Dactinomycin.
L-asparaginase.
Hydroxyurea.
Procarbazine.

CHEMOTHERAPY IN BREAST CANCER

The precise indications for the use of cytotoxic drugs become less well defined because these improve-ments are less dramatic in women over 50 years age group. Treatment decisions are made on individual patients basis.

Chemotherapy can be used as curative in cases where the tumor is not advanced and is sensitive to chemotherapy alone or in combination with other treatment modalities. A combination of chemo-therapeutic agents may be used for better results. No single agent has yet been found out to cure cancer breast at any stage.

Chemotherapy improves cure rate in primary disease of breast. It reduces the annual risk of death by 15% and has a proven benefit by various trials.

The chemotherapy can be used after surgery and/or radiotherapy for control of wide spread malignant disease. It helps to control the micro-metastasis not diagnosable by any investigation at present.

Chemotherapy in breast cancer can be given as;

NEO-ADJUVANT THERAPY

Primary systemic therapy prior to loco-regional treatment.

ADJUVANT THERAPY

It is used following loco-regional treatment.
(Post operative adjuvant chemotherapy).

The outcome of chemotherapy depends primarily on;

- Age.
- Menopausal status.
- Nodal status.
- Tumor grade.

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COMBINATION THERAPY

It is the use of multiple chemotherapeutic agents to avoid drug resistance and to achieve optimal control of cancer breast.

It is the treatment of choice in almost all types of chemotherapy whether curative, palliative, adjuvant or neo-adjuvant.

The choice of combination of drugs is determined by following factors;

- Effect of drug on target tumor type.
- Mode of action of drug on tumor (alkylating activity, mitotic inhibition activity).
- Mechanism of drug resistance.
- Dose limiting toxicity.
- Compatible dose schedule.

Combination chemotherapy is more effective than single drug therapy.

Most commonly used regimen is CMF (cyclophos-phamide, Methotrexate, 5-Flurouracil).

It is given in six cycles at monthly interval. There is no evidence that more than six months treatment is of any benefit.

It has shown to achieve a 30 percent reduction in the risk of relapse over a 10-15 year period.

The overall 10 years mortality reduction for women under 50 years is 12 percent

Impact of chemotherapy on breast cancer survival 10 years survival[2].

	Node Positive		Node Negative	
Age Less than 50 yrs	No. Chemo	Chemo	No. Chemo	Chemo
	42	53	71	78
50-69 yrs	46	49	67	

Fall in death rate% in UK & USA (1987-97)[1]

Age	UK	USA
20-49	22	19
50-69	22	18
70-79	12	9

Greatest benefit of chemotherapy is seen in pre-menopausal women (where its effect is likely to be due in part to a chemical castration effect) but is being increasingly offered to post menopausal women with poor prognosis disease.

Other combination regimens used include;

(AVM) Adriamycin, Vincristine and methotrexate.

(VCF) Vincristine, Cyclophosphamide and 5-Fluorouracil.

combination or with hormones before considering surgical treatment. These are the same drugs which are used after surgery.

Their use before surgery helps to downstage the tumor. The quality of surgery improves. The surgery becomes less extensive and more effective. The spread of malignancy is minimized. The control of malignancy is better.

It shrinks tumor often allowing breast conserving surgery rather than mastectomy (followed by post operative adjuvant chemotherapy).

Chemotherapy or use of anti-cancer drugs for cancer of breast has a major role in the control of disease. It prolongs life and controls symptoms in advanced cancer breast.

Neo adjuvant therapy has become a standard treatment in the management of locally advanced breast cancer.

Patients with earlier stage disease may also benefit from neo-adjuvant therapy in terms of improved rates of breast conserving surgery and better quality of life.

Gemcitabine is a pyrimidine analogue that has shown activity in a variety of solid tumors, a good toxicity profile and non overlapping toxicity with other chemotherapeutic agents. Preliminary findings demonstrate increased complete response rates, good tolerability in patients of cancer breast[5]. 70% tumors show a clinical response. The clinical response is complete in 20-30%.

80% of these patients still have histological evidence of tumor.
Surgery is required even in those with complete clinical response

Primary systemic therapy has not to date been shown to improve survival.

ADJUVANT CHEMOTHERAPY

It is the use of chemotherapeutic drugs after surgical treatment. It is used in patients at intermediate or high risk of recurrence. Usually these patients are offered 4-8 cycles of multiple agent (combination) chemotherapy.

The role of systemic treatment to improve outcome in operable breast cancer is clearly established. It has been shown that women under 50 years with node positive cancers show enhanced survival by 25% after addition of chemotherapy.

Systemic adjuvant treatments include cytotoxic and hormonal therapy.

Tamoxifen has shown similar increase in survival in women above 50 years age with node positive cancer breast.

Women with node negative breast cancer also get benefitted from

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figures for node positive and negative patients of 6% and 2% respectively (approx 11% relative mortality reduction).

Anthracycline containing chemotherapy combina-tions result in absolute survival benefit at 5 years of 3%.

Taxane paclitaxel may further improve the survival[3].

Commonly used chemotherapy includes Cyclophos-phamide, Methotraxate, 5 Fluorouracil, doxorubacin and epirubicin.

The anthracycline containing regimens are slightly superior and the addition of taxane to an anthracycline containing regimen may further increase the efficacy of adjuvant chemotherapy.

The patients with metastatic disease cannot be cured. The objectives of treatment are to improve the quality of life and prolong survival. Upto 60-80% of these patients experience good response to first line combination chemotherapy. The best results are achieved with 2nd and 3rd line chemotherapy drugs such as Capecitabine, Vinorelbine, Emcitabine, 5-fluorouracil and variety of its oral pro-drugs.

Combination of chemotherapy with various response modifiers is a rapidly developing field of clinical cancer research[4].

Patients with risk factors such as high grade or large size tumor that for both node negative and node positive patients also benefit from chemotherapy upto 70 years of age. The effect on outcome decreases with increase in age.

RESPONSE RATE(RR)

It is the measurement of chemosensitivity. It is used in palliative chemotherapy.

A complete tumor response represents documented resolution of all known disease for at least 4 weeks with no new lesion development.

PARTIAL RESPONSE (PR)

A partial tumor response is a reduction in the cross sectional area of measurable tumor (disease area) by more than 50% with no new lesion development.

The reduction in tumor size may relieve symptoms subjectively even in the presence of disease process.

Response rate represents survival benefit correctly as survival benefit is restricted to patients with substantial and durable tumor response.

The potential benefits must be carefully balanced against the risks of toxicity.

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Interactive consent of patient after detailed discussion of various treatment options.

Outcome monitoring strategies and record of toxic responses and criteria for treatment continuation.

ADMINISTRATION

The chemotherapy is given to achieve beneficial effects and avoid its severe side effects. The chemotherapy regimens are scheduled at 3-4 weeks intervals to allow regeneration and recovery of bone marrow.

The cytotoxic drugs are given in intravenous bolus doses over 1-2 hours or long infusions over 24-48 hours to improve efficacy and reduce toxicity. Infusion pump may be more helpful for the continuous infusion of drugs like 5 fluoro-uracil.

Vinca alkaloids can cause severe skin necrosis and loss due to extra-vasation. Skin grafting may be required to achieve adequate healing.

REGIONAL CHEMOTHERAPY

Chemotherapy can be used regionally for local treatment of tumors. High doses of chemotherapy are delivered to the tumor locally to show greater effect and low systemic toxicity.

High dose chemotherapy with stem cell rescue produces no overall survival benefit.

These can be delivered through various routes;

INTRA THECAL CHEMOTHERAPY

Intra CSF infusion of chemotherapy has been used for treatment of leptomeningeal metastatic disease.
It can also be used for the treatment of leukemia and lymphomas.

HEPATIC ARTERY CHEMO EMBOLIZATION

Liver metastasis can be palliated by chemo-embolization of liver. Chemotherapy via intra arterial injections has hardly shown any advantage in the treatment of liver metastasis.

GENERAL SIDE EFFECTS

Following side effects occur with most of the cytotoxic agent;

- Nausea and vomiting.
- Bone marrow toxicity (Suppression).
- Gastrointestinal toxicity.
- Alopecia.
- Gonadal effects.
- Hyperuricaemia.

SPECIFIC SIDE EFFECTS

Some side effects are specific to certain agents.

particular drugs. The toxic effects vary with the dose and type of drugs and schedule of administration;

FATIGUE

It may be profound and disturbing. It may effect patient compliance for next cycle. The patient must be counseled about it and measures should be taken to relieve it.

All types of side effects must be informed to the patient before starting the treatment.

BONE MARROW SUPPRESSION

It is the most serious side effect of chemotherapy. Myelo-suppression is usually at its maximum 10-14 days after treatment. It may lead to life threatening neutropenia related infections. The patient may end up in septicaemia and septic shock. All patients on chemotherapy, when feel unwell and have fever must be treated actively for septicaemia.

Thrombocytopenia occurs and presents with bruising, petechia and epistaxis. Prophylactic platelets transfusion is considered to avoid the risk of post chemotherapy hemorrhage.

Anaemia is quite common and is seen few weeks after chemotherapy. It can be treated with blood transfusion. Haemopoitic growth factors after alternate to transfusion and protection against myelo-suppression. This treatment is only cost effective in patients requiring intensive treatment with curative intentions.

HAIR LOSS (ALOPECIA)

It is a common complication of cytotoxic chemo-therapy. Alopecia may be complete within few weeks after starting chemotherapy. The hair loss can be prevented by using a cool cap over the head at the beginning of chemotherapy. The cool cap is a hat or cap which is cooled gel filled in a freezer prior to use. 70% of patients can be protected from having hair loss. The patients with liver secondaries usually have no effect with this cap and loose hair anyway.

NAUSEAAND VOMITING

These are common with cisplastin and other alkylating agents. Anti emetics are used with initial treatment in these patients. It can be relieved by granisterion, metoclopramide and domperidone for few days after chemotherapy. Delayed vomiting may be treated with corticosteroids. Intractable vomiting is uncommon but may be treated with pheno-thiazines (levomepromazine).

Most of the acute adverse effects of chemotherapy are transient. The late adverse effects are irreversible such as cardiomyopathy associated with anthracyclines. Infertility may occurs due to premature menopause of

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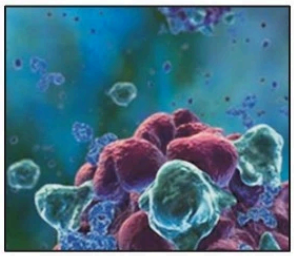
Chapter-22

Treatment Modalities - 5
Immunotherapy

Objectives

- To understand the immunological aspects in breast carcinoma patients.
- To evaluate the effects of Immunological therapy on breast cancer patients.
- To find out new immunotherapeutic agents for more effective



TREATMENT MODALITIES - 5 IMMUNOTHERAPY

Shuja Tahir, FRCS, FCPS

It is the treatment of carcinoma of breast through immune response as a part of body's natural defense or following artificial stimulation of immune system against carcinomatous tissue.

The concept of immunotherapy of cancer was evoked more than a century ago by W. Coley. Recent understanding of molecularly defined therapeutic approaches and efforts required to place immunotherapy beside surgery, chemotherapy and radiotherapy as 4th option

Its two aspects are being focused;

- Active therapeutic vaccination
- Active vaccination with allogenic bone marrow cell transplantation.

Immunotherapy is likely to be very powerful and less harmful modality than conventional therapies[4]. It is still in early stages of development.

There is relatively minor role of immunotherapy in carcinoma breast at present but future holds a very significant and positive role of this modality for the treatment of carcinoma breast.

The immune system can clearly recognize the cancer cells. There is little evidence that it does so to any effective consequence in patients with advanced breast cancer.

The challenge for the clinician is to find ways to enhance the ability of a patient's own immune system to recognize and effectively target malignant cells. There is no shortage of target antigens for immune cell recognition of breast cancer.

It is still not clear whether successful outcome depends upon enhanced recognition of an individual target or a more general route to enhance immune cell activation[2]

A variety of specific and non specific immuno stimulatory strategies have been applied with only modest clinical success.

The molecular characterization of novel human tumor antigen and improved understanding of immunological

rejection antigens. Identification of antigen specific T and B cells will be helpful in clinical and diagnostic immunotherapy[3].

There is increasing evidence that tumors express putative target molecules for therapeutic immune reaction. The identification of immunogenic tumor associated antigens may allow new modes of vaccination with a hope to add a new and powerful modality for treatment of cancer breast[13].

Adjuvant chemotherapy has achieved significant result but the control of minimal residual cancer breast is still a challenge for treating clinicians.

Immunotherapy holds promise for future modes of treatment. This anti cancer strategy aims at triggering a highly specific endogenous killing machine against tumor cells[14].

Many clinical observations are suggestive of immunological recognition of human cancer such as;

The tumors of breast are recognized by the body as foreign to the host.

The halo naevus a surrounding area with prominent lymphocytic infiltrate suggesting endogenous immune response.

Spontaneous regression of cancers is also suggestive of striking endogenous immune response.

Histological examination of regressing lesion show significant T-cell infiltration.

Spontaneous regression after resection of primary tumor is seen in renal cell carcinomas and melanomas possibly due to immunological response of the body against cancer.

Acquired immune deficiency or dysfunction is related with increased incidence of malignancies.

Two clear components of immune system are noticed in cleaning the foreign matter (cancer tissue and microbes);

- Non specific immune response (phagocytosis and inflammation).
- Specific recognition by humoral and/or cellular immunity.

T-cells differentiate in thymus and mediate cellular response.

B-lymphocytes produce immunoglobulins in response to foreign antigens. The immunoglobulin-antigen combinations trigger cellular and molecular response.

Macrophages, mononuclear phagocytes and dendritic cells are the antigen presenting cells.

Lymphocytes are natural killers. These destroy tumor cells coated with

few clinical responses. Some chemotherapeutic agents may enhance the immune effects of genetically modified tumor vaccines[6].

Tumor vaccines are based on weakly immunogenic specific tumor antigens admixed with adjuvants in order to elicit, restore, augment anti tumor immune responses against residual or metastatic tumor cells. Cellular cytotoxity plays major role in killing tumor cells.

It requires three synergistic signals;

1. Presentation of specific tumor antigen.
2. Costimulatory signal (B-7 molecules).
3. Propagation signal cytokines.

Vaccines produce specific immune response and objective clinical responses with minimal toxicity.

Advances in gene transfer technology, tumor immunology and better methods of monitoring specific anti tumor response promise a hope for future development of tumor vaccine for appropriate clinical use[7].

The major immunotherapeutic strategies have potential to enhance or generate an anti breast cancer T-cell immune response;

1. Cytokine therapy.
2. Cancer vaccines.
3. T-cell therapy[12].

INTERFERON

There are three classes of interferon α, β and γ. These pose wide spectrum of activities. These are antiviral, stimulatory to immune system (macrophage phagocytosis, natural killer cells and direct cytotoxic effects). These change cell membrane characterisitics of the tumor cells.

These function by binding to cell surface receptors interacting with specific gene sites in normal and neoplastic cells.

INTER LEUKINS

These are peptides which act as modulators of immune and inflammatory response. Interleukin 2 (IL-2) is a natural product secreted by activated CD4-positive T-lymphocytes.

IL-2 stimulates production of interferon γ and tumor necrosis factor (TNF) it activates natural killer cells, lymphocyte activated killer cells (LAK). These kill tumor cells.

HERCEPTIN

It is a recombinant, humanized monoclonal antibody. It is an immune therapeutic agent which has attracted significant attention because of its efficiency and moderate toxicity.

Herceptin given in combination with chemotherapy for advanced breast cancer has a higher response rate and longer disease free survival than chemotherapy alone in women with HER-2/neu positive tumors (survival advantage).

Local and systemic treatment for cancer breast such as surgery, radiation therapy, hormonal therapy and chemotherapy are effective against primary and metastatic disease but far from achieving cure and survival of patients. It may be due to emergence of drug resistant tumor cells.

Gene therapy offers a useful approach to breast cancer therapy. These approaches are;

Altering the metabolic or signaling response within the breast cancer.

Designed to enhance the immune response to tumor cells (immunogene therapy)

Using the drug resistant gene with chemotherapy.

The systemic treatments are more important. It is hopeful to over come the difficulties like heterogenicity and low immunogenicity of breast cancer cells[11].

DENDRITIC CELLS

Dendritic cells play a major role in the generation of immunity against tumor cells. These can be grown under various culture conditions which influence the phenotypical and functional properties immune response mainly executed by T-cells. Administration of dendritic cells cause tumoricidal T-Cell based immune response[5].

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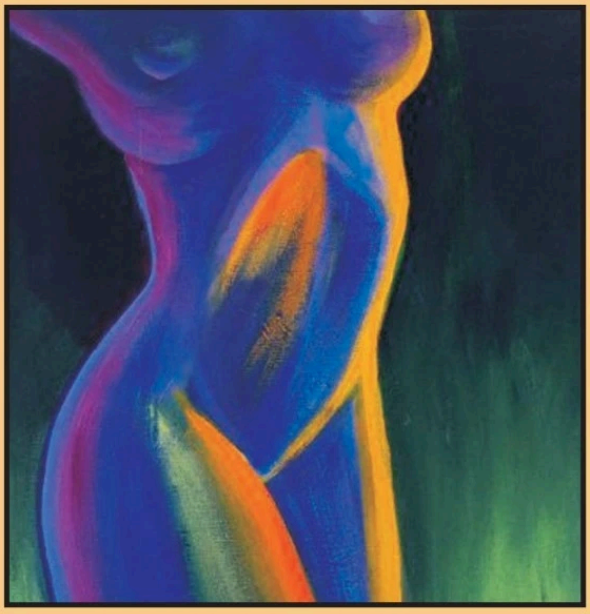
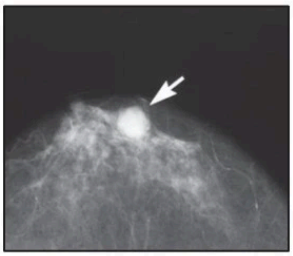
Chapter-23

Prognosis in Cancer Breast



Objectives

- To understand the tumor biology.
- To understand the natural behavior of tumor.
- To understand the outcome of various treatments.
- To plan preventive measures to improve the quality of life.
- To plan psycho-social aspects of patient.
- To counsel the patient adequately.



PROGNOSIS IN CANCER BREAST

Shuja Tahir, FRCS, FCPS

Prognosis is a forecast as to the probable outcome of an attack of disease. It is also the prospect as to the recovery from a disease as indicated by the nature and symptoms of the patient.

Prognosis in breast cancer is the assessment of quality and quantity of life after the diagnosis and / or treatment for cancer of the breast. Prognosis depends upon;

1. Dynamic interplay between anatomical extent of tumor and its growth potential (virulence/aggressiveness)
2. Degree of Immuno competence of the host (host defence mechanism).
3. Appropriate and timely treatment.

There are many factors, which help to predict the prognosis and estimate survival in patients with breast cancer;

- Anatomical extent of cancer
- Number of axillary nodes involved with tumor.
- Histopathological features of lymph nodes.
- Size and / or contour of primary lesion.
- Growth rate of tumor (doubling time or mitosis).
- Histologic type of tumor.
- Tumor differentiation (histologic nuclear grading).
- Extent of lymphocytic infiltration.
- Mucin secretion.
- Lipid content.
- Tumor necrosis.
- Lymphatic invasion.
- Blood vascular invasion.

ANATOMICAL EXTENT OF CANCER

Assessment of extent of tumor is performed by staging the disease. Staging of carcinoma breast is performed with great care. It is based on the fact that carcinoma breast starts locally, spreads locally and regionally to lymph glands and distant metastasis is seen as the systemic spread occurs . Most but not all patients show direct relationship to the stage of disease at the time of diagnosis and length of survival.

The earlier the cancer is detected, the better is the prognosis.

cancer patients is only 25%.

10 year survival rate in cancer breast.	
Node free cancer breast	75%
Node positive cancer breast	25%

It is not only the involvement of nodes but their number, level of involvement and extension through capsule. Determination of micro or macro metastasis are important prognostic factors.

There is 33% difference in involvement of nodes between clinical and histological assessments.

The false evaluation of axillary nodes on clinical examination varies between. (false positive : false negative 24%-39%)
Overall error in clinical staging is about 32%.
35 % of clinically negative nodes have metastasis on histopathology.
87% clinically positive nodes have metastasis on histopathology.

In pathologically negative nodes;
5 years survival 84%.
10 years survival 70%.

In clinically negative nodes ;
5 years survival 74%.
10 years survival 58%.

In pathologically positive nodes ;
5 years survival 52%.
10 years survival 33%.

In clinically positive group of nodes ;
5 years survival 58%.
10 years survival 38%.

Description	5 year survival	10 year survival
Pathologically negative nodes	84%	70%
Clinically negative nodes	74%	58%
Pathologically positive nodes	52%	33%
Clinically positive nodes	58%	38%

The number of axillary nodes involved in cancer is inversely proportionate to patient's survival. More number of nodes involved, worse is the prognosis.

Ten years survival ranges between 38-54% when one to three nodes are involved but it drops to 13% when more than three nodes are involved,

Five year survival Level wise	
Level-I involvement	65%
Level-II involvement	45%
Level-III involvement	28%

patients is about 49%. It is not only the number but the level of nodal involvement as well which affects prognosis signifi-cantly.

contained within capsule has 30% recurrence rate after same period.

Lymph node morphology has variable prognosis (10 years survival) such as;

10 years survival (lymph gland morphology)	
Lymphocyte predominance	75%
Germinal center predominance	54%
Lymphocyte depletion	33%
Un stimulated	37%

The prognosis (5 years survival) is decreased as the size of carcinoma increases, (local spread, T-staging).
The lymph gland involvement (N staging regional spread) affects the prognosis badly.

Smaller the cancer, better the survival.

Non invasive carcinoma of breast (lobular carcinoma and intra ductal carcinoma) and early invasive cancers (minimal cancers) upto 0.5 cm diameter have an estimated ten year or more survival over 90%.

Cancers less than 01 cm size are termed as minimal cancers. These show 20 years survival rate of about 93% and 10 years survival rate of 95%.

SHAPE OF CANCER BREAST

Cancer margins (contour or configuration) affects prognosis. The rounded tumour has better 10 years survival and tumors with irregular margins have poor prognosis.

SITE OF CANCER

Cancer of breast present in the outer quadrants has better prognosis than if present in the inner quadrants.

5 years survival in medial quadrant tumours is 70%.
And 5 year survival in lateral quadrant tumour is 84%.
It seems to be due to involvement of internal mammary lymph glands which affect the prognosis significantly.

The prognosis is poor when tumours are located in the middle vertical segment of the breast or are diffuse.

There are different types of cancer breast. Some lesions have less virulence and rarely change to metastatic disease. Some are very virulent and change into metastatic disease early. These two groups have marked difference in the prognosis and mortality.

40% of accurately diagnosed patients of carcinoma breast die at a rate of 25% per year (Aggressive tumors). 60% of patients die at the rate of 2.5% per year (less aggressive tumors).

The patients with local breast cancer and no lymph node involvement have

situ (LCIS) and intra ductal carcinoma in situ (DCIS) have excellent prognosis (100%) 5 years survival.

These patients usually do not have any recurrence when treated with simple mastectomy and axillary sampling.

Following histologic types of invasive carcinoma of breast have better prognosis ;

Adenocystic carcinoma.
Colloid carcinoma.
Comedo carcinoma with minimal stromal invasion.
Medullary carcinoma with lymphoid infiltrate .
Papillary carcinoma.
Tubular carcinoma.

5 year survival in cancer breast	
Quadrant	
Medial (Inner)	70%
Lateral (outer)	84%

NUCLEAR GRADING I (NG-I)

There is definite association between nuclear grading and survival of the patient. It shows marked variation in size and shape; differentiation and general or nuclear grading.

Prominent nucleoli.
Chromatin clamming.
Numerous mitotic figures.

It is considered to be undifferentiated.

NUCLEAR GRADE II (NG-2)

It is intermediate grade between NG -1 and NG-3. The nuclear changes are moderately differentiated.

NUCLEAR GRADE III (NG-3)

The nuclei are quite similar in size and shape to normal breast cell nuclei. These are well differentiated with minimal malignant change.

TUMOR GROWTH AND AGGRESSIVENESS

The doubling time of breast cancer cells vary between 23-209 days with an average of 100 days.

A tumor with 23 days doubling time takes about 2 years to attain 1 cm size.

A tumor with 200 days doubling time takes 17 years to achieve size of 1 cm.

Majority of patients show inverse relationship of survival to the size of tumor at time of diagnosis but in some cases post operative survival of patients with large size tumor is prolonged while of those with small size tumor is minimized with disseminating

TUMOR NECROSIS

Tumor necrosis is associated with greater rate of regional (axillary metastasis). It has higher mortality.

Tumors with necrosis and infiltrated border are more aggressive and have 75% rate of axillary metastasis. It is associated with 29% 10 years survival.

Tumors with smoothly circumscribed borders and no necrosis have 30% rate of axillary metastasis and 61% 10 years survival.

Tumor necrosis is an independent variable predicting treatment failure.

SPREAD OF TUMOR

Blood vessel invasion by tumor has a negative effect on survival time. Blood vessel invasion is more likely to be associated with a severe cell reaction in the tumor, lymphatics, invasive metastasis, four or more axillary nodes, necrosis and NG I grading.

Lymphatic invasion is an unfavourable pathologic finding for patients survival. There is an association of early tumor recurrence at 6-18 months.

Tumors with perineural space invasion are more likely to be associated with lymphatic invasion, nipple involvement and axillary metastasis.

Tumor recurrence is seen early in these patients (within 18 months).

Although it is not confirmed yet, elastosis present in the tumor bed is a favourable sign and has better 5 year survival. It is a sign of slow growth of tumor.

Mucinous or colloid carcinoma of breast has favourable prognosis but intracellular mucin (signet ring cell) carcinoma does not have better survival.

Good host defense response to cancer is indicative of better survival.

LYMPHO-RETICULOENDOTHELIAL RESPONSE

The fatal behavior of carcinoma of breast is determined by the interaction of growth potential of tumor nuclear grade or relating to host inhibitory or resistance factors that represent an immunological response of reticuloendothelial system.

These include the degree of lymphoid infiltrate around the tumor, the degree of perivenous infiltrate in section cut through the tumor, number of histiocytes in the sinusoids of regional lymph nodes (sinus histiocytes).

These tests are graded 0-4 with better survival in higher grades and worst in lower grades.

IMMUNO COMPETENCE OF PATIENT

shorter the time of disease free interval, greater is the number of sites of recurrence, poorer is the survival.

Recurrence in liver and brain has extremely poor prognosis while recurrence in bones have less poor prognosis. Untreated patients of breast cancer have a 5 year survival of 18% and 10 years survival of 4%. Any Form of treatment is likely to improve survival.

The primary objective of the treatment of carcinoma breast is cure. Although cosmetic appearance and functional results are very important, no procedure is selected to compromise cure of the cancer.

Earlier the diagnosis is confirmed, better is the cure and long term survival.

Early diagnosis offers better cure, less extensive surgery, better cosmetic results, less adjuvant therapy and better functional results.

The morphometrical grading system helps in efficient prediction of prognosis of cancer breast by dividing patients into;

Favourable (grade I).
Intermediate (grade II).
Unfavorable (grade III).

Morphological grading is efficient in identifying patients with most unfavorable outcome. Morphometrical grade III patients have a 5.4 fold risk of breast cancer death[1].

Breast cancer comprises 22% of all cancers occurring in females but only 2% of cases occur in women aged 35 years or less[2].
Breast cancer in young (<or=35 years) women is biologically aggressive compared with older women. Factors predicting survival and overall survival are comparable with those of old women.

Difference between 5 year survival rate is observed according to length of

5 years survival rate depending upon length of interval between diagnosis and recurrence.

Shorter than 24 months	14%
24-60 months	64.3%
More than 60 months	41.7%

Patients with interval;
Shorter than 24 months has survival rate 14.3%.
Between 24-60 months survival rate 64.3%.
Longer than 60 months had 41.7%[3].

Patients treated with surgical excision and chemoradiation have better prognosis about 53.9% than patients who could not have surgical excision.

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Chapter-24

Primary Care for Survivors of Breast Cancer

Objectives

- To evaluate the outcome of treatment in breast cancer patient.
- To look after the breast cancer patient adequately.
- To look after the psycho-psychiatric aspect of the patient.
- To look after the socio-economic aspects of the patient.
- To look after and manage the complication of disease or its treatment appropriately.

RIMARY CARE FOR SURVIVORS OF BREAST CANCER

Faisal Bilal Lodhi, FCPS

Screening programs have increased the number of women in whom invasive or noninvasive breast cancer has been diagnosed. Earlier detection and better treatment have led to improved prognosis.

Women with breast cancer have several unique health issues. They require regular follow-up to detect recurrences of their breast cancer at the earliest. They may have long lasting side effects of treatment including premature menopause. Survivors of cancer may have questions regarding childbearing, the use of hormone replacement therapy, psychological and social aspects of survival.

MEDICAL EVALUATION

Women with a history of breast cancer are at risk for recurrence for the rest of their lives,. Most of these are detected within 5 years, but recurrences can occur 5 to 10 years after diagnosis and later recurrences are not uncommon. Symptoms suggestive of recurrence include;

- Changes in the breast or chest wall.
- Adenopathy (axillary and other).
- Weight loss.
- Persistent cough.
- Cardio-pulmonary symptoms.
- Musculo-skeletal pain.
- Headache and vertigo.

These symptoms are non specific and even in survivors of cancer, are frequently attributable to benign conditions. Many long term follow-up studies have shown that more than 75 percent of recurrences are heralded by symptoms or by findings on physical examination. The symptoms should be carefully evaluated[1,2].

Physicians may detect local or regional recurrences in the breast, chest wall or lymph nodes on physical examination. Laboratory tests, chest roentgenography and bone scanning. They rarely identify metastatic disease in asymptomatic patients.

Even with intensive surveillance, asymptomatic recurrences constitute only a fraction (15 to 25%) of all cases of metastatic disease[3].

Modeling studies suggest that patients with node-negative breast cancer who are known to carry a BRCA1 or BRCA2 mutation may have gains in life expectancy from prophylactic contra lateral mastectomy. In addition, the family members of affected patients may want to consider intensive surveillance or prophylactic surgery.

LOCAL COMPLICATIONS OF THERAPY FOR BREAST CANCER

Local complications are worse with more extensive surgery, more extensive radiation or both and may be aggravated by adjuvant chemotherapy.

Breast reconstruction with implants or tissue flaps is an option for most women after mastectomy. The reconstructed breast should be examined for nodular, erythematous or rash like changes in the skin or subcutaneous tissues that might indicate recurrence.

Women who are candidates for radiation therapy after mastectomy may wish to consider reconstruction with autogenous tissue or delay reconstruction. Radiation therapy contributes to complications and impairs cosmoses after construction, particularly when implants are used[8].

Lymph edema rates of 10 to 25% are still reported, although most cases are mild. The risk of lymph edema is directly related to the extent of axillary surgery and radiation treatment.

Because it requires less extensive axillary surgery, sentinel-lymph node biopsy is likely to be associated with a lower risk of lymph edema than standard axillary dissection.

Obesity, weight gain and infection in the arm are additional risk factors for lymph edema. In most patients, lymph edema responds to conservative management, including arm elevation and the use of compression gloves or sleeves. Appropriate physical therapy may relieve lymph edema that does not respond to conservative treatment. It is reasonable to protect the ipsilateral arm from infection, compression, venipuncture, exposure to intense heat and abrasion to minimize chance of lymph edema.

LATE COMPLICATIONS OF CHEMOTHERAPY

Chemotherapy for breast cancer have many adverse effects, most of which resolve after treatment has been completed. The most serious, even life threatening, late sequelae are secondary leukemia and cardiac impairment, both of which are rare. Clinically significant congestive heart failure develops in 0.5 to 1.0% of women treated with standard anthracycline based chemotherapy regimens.

Risk factors for cardiac toxicity include

-phamide, methotrexate and fluorouracil or anthracycline adjuvant chemotherapy.

GYNECOLOGIC AND REPRODUCTIVE COMPLICATIONS OF THERAPY

AMENORRHEA RELATED TO CHEMOTHERAPY

Adjuvant chemotherapy is frequently associated with either temporary or permanent amenorrhea resulting from direct toxicity to the ovary. The incidence of chemotherapy induced ovarian failure depends on;

The chemotherapy regimen.
The cumulative dose.
(particularly the dose of alkylating agents such as cyclophosphamide).
The age of the patient.
Younger women are much less likely to have chemotherapy induced amenorrhea. On the other hand, ovarian failure is common in women over 40 years of age who are receiving chemotherapy.

Chemotherapy induced ovarian failure is characterized by diminished circulating levels of estrogen and progesterone and elevated levels of follicle-stimulating hormone and luteinizing hormone. These changes are similar to the changes seen in natural menopause and have the same effects. Because of the rapid change in menopausal status, symptoms can be more severe than those associated with the more gradual lowering of estrogen levels that occurs with normal aging.

EFFECTS OF TAMOXIFEN ON GYNECOLOGIC FUNCTION AND FERTILITY

Tamoxifen is a mixed estrogen against and antagonist that has a variety of effects on gynecologic functions. Among both younger and older women, tamoxifen therapy can cause hot flushes, night sweats, vaginal discharge, itching or dryness. Over half of all women taking tamoxifen report such symptoms, although in most cases they are mild. Tamoxifen may contribute to dyspareunia and can diminish sexual interest and satisfaction.

Menstrual function may be either normal or disrupted during tamoxifen therapy. Women who have menstrual dysfunction while taking tamoxifen may resume normal menses after drug therapy is stopped.

Women who wishes to become pregnant should discontinue tamoxifen therapy several months before trying to conceive.

Tamoxifen increases the risk of endometrial cancer, owing to its proestrogenic effects on the endometrium[10]. The risk is more pronounced among postmenopausal women, obese women, and women who have had hormone replacement therapy. Endometrial cancer develops

become pregnant after a diagnosis of breast cancer have a worse outcome then those who do not become pregnant.

Self selection of patients with a more favorable prognosis on the basis of tumor features or natural history may introduce bias into studies of pregnancy after a diagnosis of breast cancer.

According to the limited available reports, previous chemotherapy does not appear to have teratogenic effect[11].

The studies to date offer reassurance for women who wish to become pregnant after treatment for breast cancer, but they do not exclude the possibility that, for a given patient, pregnancy may increase the risks of recurrence.

Traditionally, patients have been advised to wait two years after diagnosis before becoming pregnant, because of the higher rate of recurrence of breast cancer in the first several years.

The extent and nature of breast conserving surgery affect the likelihood of successful lactation. Resection of centrally located tumors is more likely to impair lactation, as is breast irradiation which causes fibrosis of the lobules.

A breast that has been treated by breast conserving surgery and irradiation may not undergo hypertrophy during pregnancy resulting in asymmetric breast enlargement.

Some women (25 to 30%) are able to lactate after breast conserving surgery and irradiation, but the majority of these patients continue to report difficult and inadequate lactation in the affected breast.

HORMONE REPLACEMENT THERAPY

Surveys suggest that a minority of survivors of breast cancer (20 to 30%) are interested in hormone replacement therapy and that these are mainly women with severe menopausal symptoms or a great fear of heart disease or osteoporosis.

Hormone replacement therapy is generally not recommended for survivors of breast cancer, partly because of the possible risk that such therapy will exacerbate breast cancer and partly because any potential benefits of such therapy are diminished by the risk of death from breast cancer in these women.

Furthermore, Hormone replacement therapy can impair both the sensitivity and the specificity of mammography potentially impeding the timely detection of a new contra lateral breast cancer or an ipsilateral recurrence.

Consideration of Hormone replacement therapy seems most reasonable in the small subgroups of survivors of breast cancer including;

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months) is likely to be safer than extended use[8].

OSTEOPOROSIS & CARDIOVASCULAR RISK FACTORS

survivors of breast cancer may be at lower risk for osteoporosis than the general population because of the role of estrogen in both preserving bone mineral density and increasing the risk of breast cancer. However clinical trials have demonstrated that amenorrhea caused by adjuvant chemotherapy is accompanied by a loss of bone mineral density of 2 to 7%, a loss similar to that which occurs during natural menopause. As with normal menopause, trabecular bone (such as the lumbar spine) is affected more than cortical bone (such as the femoral neck).

Specific interventions may alter the risk of osteoporosis in survivors of breast cancer.

Tamoxifen preserves bone density in postmenopausal women by its proestrogenic effects[10] and may reduce the incidence of osteoporotic fractures of the hip, spine and radius. In premenopausal women, however, tamoxifen therapy has been associated with varying degrees of loss of bone mineral density. Bisphosphonates, given either during or just after adjuvant chemotherapy, may prevent the loss of bone mineral density associated with chemotherapy induced menopause, as they do in the general population of postmenopausal women.

Survivors of breast cancer may benefit from other strategies to minimize the risk of osteoporosis, such as smoking cessation, treatment of any metabolic or endocrine disorders, weight bearing exercise and adequate intake of calcium (1000 to 1500 mg/day) and vitamin D (400 to 800 IU/day).
There is concern that prolonged estrogen deprivation may put survivors of breast cancer at greater risk for heart disease. As yet, there are no data on the clinical importance of estrogen deprivation in such women.

Aggressive and appropriate management of known risk factors for cardiovascular disease, such as hypertension, diabetes, and elevated lipid, as well as the encouragement of smoking cessation is clearly warranted with modern techniques of radiation therapy. The risk of cardiac disease due to irradiation of the left side of the chest appears to be minimal. Women treated according to older radiation protocols and with older equipment may have a slightly increased long term risk of cardiac complications from irradiation of the breast or chest wall.

Tamoxifen therapy is associated with an increased risk of thromboembolic events, including deep venous thrombosis, pulmonary embolism and stroke. The absolute risk is small (these events occur in 0.5 % of patients) but is

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dyspareunia, incontinence and vaginal dryness. Estrogen rings appear to be associated with less systemic absorption of estrogen than oral or topical estrogen, but the safety of locally applied estrogen in survivors of breast cancer is not known.

PSYCHO SOCIAL ISSUES

The diagnosis and treatment of breast cancer is life altering event with significant psychological impact on patients, families and friends.

Specific treatments for cancer and the experience of having a serious illness contribute to psychosocial difficulties. Clinicians should inquire about mood disorders, fatigue, anxiety, impaired cognitive performance and sexual dysfunction, since these problems are prevalent among survivors of breast cancer.

Psycho social distress and problems with adjustment are most intense during the first year after diagnosis and therapy and they tend to improve over time.

Risk factors for more pronounced psychological and social distress include;

Preexisting psycho-social, family or marital stress.
Intense initial response to diagnosis and treatment.
Young age.
Negative body image.
Treatment related side effects (e.g. menopause, limb edema etc[10].

Most of these impairments resolve with time and adequate psychological support by the treating clinician.

Survivors of breast cancer identify many positive aspects of life after diagnosis of cancer, including an optimistic outlook on life and a renewed sense of confidence, purpose and vitality.

CHANGES IN LIFESTYLE

Obesity and weight gain, a lower level of exercise and physical activity and greater alcohol consumption are all associated with a higher risk of breast cancer. It is not known whether modifications in lifestyle or diet after a diagnosis of breast cancer improve survival.

Women who are treated with adjuvant chemotherapy particularly those who go through early menopause often gain weight. Tamoxifen does not appear to contribute to weight gain.

Multi disciplinary efforts, including nutritional advice, counseling and exercise, can help survivors of breast cancer lose weight. Moderate exercise programs have been shown to lessen fatigue, as well as the symptoms of depression and anxiety among survivors of breast cancer.

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Chapter-25

Epidemiology & Biostatistics in Cancer Breast

Objectives

- To understand various scientific and statistical definitions.
- To be able to analyze various health conditions.
- To compare the local scientific data with data from other parts of the world.

EPIDEMIOLOGY & BIOSTATISTICS IN CANCER BREAST

Shuja Tahir, FRCS, FCPS

INCIDENCE

It is the number of new cases of cancer breast in a defined population during a given period (defined period) of time. It is expressed as rate / number of population / year.

It is calculated by the formula;

Number of new cases of cancer breast in a given time period
x 1000
Population at risk during that period

SUSCEPTIBILITY

Susceptibility means a likelihood of a person getting a disease.

PREVALENCE

It is the total number of cancer breast patients present in a defined population during a given period of time.

MORTALITY

It is the number of deaths due to cancer breast in a defined population during a given period of time.

It is expressed as rate / number of population / year.

MORBIDITY

Morbidity is defined as a change, subjective or objective from phsiological well being. It can be measured in;
Number of persons who were ill.
Spells / Periods of illness experienced by persons.
Duration of these illnesses.

ENDEMIC DISEASES

It refers to the constant presence of a disease within a given geographic area or population group without importation.

It also refers to the usual or expected frequency of the disease with such area or population group.

SPORADIC DISEASES

It refers to the disease process which is scattered. The cases occur irregularly, haphazardly from time to time. These cases are few in number and separated

examinations or other procedures in apparently healthy individuals who are not seeking help from health care. It could be mass screening, high risk screening, selective screening or multiphasic screening.

Screening tests are not intended to be diagnostic. These help in picking up the positive case for further diagnostic work up. The time gained by screening for early detection of cancer breast is called lead time.

LEAD TIME

Lead Time is the period between diagnosis by early detection (screening) and diagnosis by other means.

EPIDEMIOLOGY OF BREAST CANCER

It is the presence and behavior of carcinoma breast in a defined population during the defined period which can be mentioned and compared in relation to the characteristics of that population.

It is used to explore factors related to cancer breast etiology and risk factors by virtue of race, exposure to known genetic, environmental & cultural risk factors.

EPIDEMIOLOGICAL SIGNIFICANCE

Cancer of breast is rare in men but most common in women. There is 3% increase in the incidence annually. The incidence, mortality and survival trends in breast cancer have changed after the use of mammographic screening. There is clear difference in the behaviour of pre and post menopausal cancer breast.

The cancer breast arises from ductal or lobular epithelial cells with many histological sub groups. There is marked variation in incidence between races, geographical areas and socio-economic groups.

The rates are almost double in north America and Israeel when compared with Eastern Europe, Singapore & Philippines & three times when compared with China, Japan, India & Pakistan.

40% of families with increased cases of cancer breast and more than 80% of families with breast and ovarian cancer are due to genetic mutation & BRCA I gene. These account for 4% of all breast cancers.

MAJOR RISK FACTORS

- Early menarche.
- Late menopause.
- Late first birth.
- Single women.

MINOR RISK FACTOR

- Post menopausal obesity.

SENSITIVITY

It is ability to identify effected individuals in screened population.
It is the ability of a test to identify correctly or to pick up correct diagnosis.
It is the ratio of true positive (TP) to the total of true positive and false negative (FN) patients.

$$\text{Sensitivity} = \frac{TP}{TP+FN} \times 100$$

SPECIFICITY

It is the degree of correlation of positive test to the presence of disease.
It is the ability to differentiate disease process correctly.
It is the identification of those who truly do not have the disease.

This is the ratio of true negative (TN) to the total of true negative and false positive (FP).

$$\text{Specificity} = \frac{TN}{TN+FP} \times 100$$

ACCURACY (Efficiency or Validity)

It is the percentage of correct pick up or identi-fication.
It is the ratio of true positive and true negative to total patients.
It is the ratio of true positive (TP) plus true negative (TN) results to the total number of patients subjected to the test.

$$\text{Accuracy (Validity)} \quad \frac{TP+TN}{\text{Total number of patients}} \times 100$$

POSITIVE PREDICTIVE VALUE

It is the ratio of true positive to the total of true positive and false positive.

$$= \frac{TP}{TP+FP} \times 100$$

NEGATIVE PREDICTIVE VALUE

It is the ratio of true negative to the total of true negative plus false negative.

$$= \frac{TN}{TN+FN} \times 100$$

FALSE POSITIVE RATE = 100% - specificity
FALSE NEGATIVE RATE = 100% - sensitivity

PROGNOSTIC INDEX

It is an index or %age or a figure which predicts prognosis

It is calculated by the formula;

(PI) = (0.2 x size of tumor in cms) + (stage)+(grade)

Prognosis of breast carcinoma

NOTINGHAM PROGNOSTIC INDEX (NPI)

NPI = (tumor size in cms x 0.2) + Lymph node stage + tumor grade.

2= 1-3 positive nodes.
3= 4 or more positive nodes.
3= 4 or more positive nodes.

Tumor grade
1= Well differentiated.
2= Moderately differentiated.
3= Poorly differentiated.

Prognostic groups	Prognostic Index	5 years survival
Good	Less than 3.1	88%
Moderate	Bet 3.4-5.4	69%
Poor	More than 5.4	25%

NOTINGHAM PROGNOSTIC INDEX (NPI)

Prognostic Groups	N.P.I	10 yrs survival %
1- Excellent	Upto 2.4	94
2- Good	Upto 3.4	83
3- Moderate - I	Upto 4.4	70
4- Moderate - II	Upto 5.4	51
5- Poor	> 5.4	19

CASE CONTROL STUDY

It is the study of patients and control group. It reflects some kind of incompatibility.

COHORT STUDY

It is an observation or analytical study of cases. It helps to obtain additional evidence in favour or against the existing knowledge.

It is also called prospective study, longitudinal study or incidence study.

RETROSPECTIVE STUDY

Retrospective study or retrospective cohort study is one in which the outcomes have all occurred before the start of investigations.

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